Canada's Drug and Health Technology Agency

CADTH Reimbursement Review

CADTH Reimbursement Recommendation

(Draft)

evolocumab (Repatha)

Indication: Repatha is indicated for the reduction of elevated low-density lipoprotein cholesterol in adult patients with primary hyperlipidemia (including heterozygous familial hypercholesterolemia and atherosclerotic cardiovascular disease):

- as an adjunct to diet and statin therapy, with or without other lipid-lowering therapies, in patients who require additional lowering of low-density lipoprotein cholesterol
- as an adjunct to diet, alone or in combination with non-statin lipid-lowering therapies, in patients for whom a statin is contraindicated.

Sponsor: Amgen Canada Inc.

Recommendation: Reimburse with Conditions

Version:	1.0
Publication Date:	May 2024
Report Length:	21 Pages

Single Technology

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

Recommendation

This recommendation supersedes the CADTH CDEC recommendation for this drug and indication dated November 2017.

The CADTH Canadian Drug Expert Committee (CDEC) recommends that evolocumab be reimbursed for the reduction of elevated low-density lipoprotein cholesterol (LDL-C) in adult patients with primary hyperlipidemia (atherosclerotic cardiovascular disease) only if the conditions listed in **Error! Reference source not found.** are met.

Rationale for the Recommendation

In one double-blind, placebo-controlled, randomized clinical trial enrolling patients with ASCVD receiving optimized statin therapy (FOURIER, N = 27,564), a composite outcome of cardiovascular (CV) death, myocardial infarction (MI), stroke, unstable angina (UA), or revascularization was experienced by 9.8% of patients taking evolocumab and 11.3% of patients taking placebo over a median follow-up period of 26 months (hazard ratio [HR] of 0.85; 95% confidence interval [CI], 0.79 to 0.92]).

Two studies, Gencer et al. (n = 5711) and Sabatine et al. (2018) (n = 8402), reported on subgroup analyses of the FOURIER trial for patients with a recent MI, defined as MI within 1 year and 2 years, respectively. The results of the subgroup analyses by Gencer et al. suggested an increased benefit (reduced risk of CV events) with evolocumab compared to placebo, primarily for MI (experienced by 4.50% versus 6.61% of patients taking evolocumab versus placebo, HR = 0.67; 95% CI, 0.54 to 0.84) and coronary revascularization (experienced by 7.30% versus 9.79% of patients taking evolocumab versus placebo, HR = 0.74; 95% CI, 0.62 to 0.89). Although these results were not conclusive based on the statistical analyses, the prespecified subgroup analyses results on MI and coronary revascularization were consistent with the results in the overall population enrolled in FOURIER. An ad-hoc subgroup analysis of patients with prior MI in the FOURIER open-label extension (OLE) provided supportive evidence of a benefit in terms of a reduction in risk of MI for patients who received evolocumab earlier compared to those who received delayed treatment as a result of randomization to placebo in the parent trial, over a follow-up period of up to 5 years. Evidence of safety was not available by subgroups, but the evidence for treatment-emergent adverse events (TEAEs) were similar between evolocumab and placebo in the FOURIER trial and no new concerns were identified during the OLE with evolocumab alone. In particular, muscle-related adverse events (AEs) were similar between evolocumab and placebo as randomized in the original FOURIER trial, and this was noted to be important to patients.

Input from patient groups was not submitted for the reassessment of evolocumab. Based on the patient input received for the 2017 resubmission for evolocumab, patients and clinical experts both identified that access to new therapies that can reduce cholesterol levels in patients who cannot meet their cholesterol targets with available treatment options or who cannot tolerate statins is an unmet need identified as important to patients due to the association with a reduction in the risk of MI or other CV events. CDEC concluded that evolocumab may meet this need.

Using the sponsor submitted price for evolocumab and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) for evolocumab was $87,882 per quality-adjusted life-year (QALY) gained compared with optimized background lipid lowering therapy (LLT), comprising moderate-to-high intensity statin therapy with or without ezetimibe. At this ICER, evolocumab is not cost-effective at a $50,000 per QALY willingness to pay (WTP) threshold for adults with recent ACS within the past 1 year who have LDL-C ≥ 1.8 mmol/L. A price reduction is required for evolocumab to be considered cost-effective at a $50,000 per QALY gained threshold.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Adult patients with a recent ACS event, defined as a hospitalized index ACS to 52 weeks post index ACS	Subgroup analyses of the FOURIER trial provided evidence of a treatment benefit with evolocumab compared to placebo in patients with a recent ACS event, defined as a MI within 1 year (Gencer, et al.).	—
2. Patients with elevated LDL-C levels, defined as LDL-C ≥ 1.8 mmol/L or non-HDL-C ≥ 2.6 mmol/L, despite taking maximally tolerated dose of statins. 2.1. If LDL-C levels are ≤ 2.2 mmol/L or non-HDL-C ≤ 2.9 mmol/L, patients must have demonstrated an adequate trial of ezetimibe prior to initiation of evolocumab 2.2. Evolocumab can be initiated with or without ezetimibe if LDL-C levels are > 2.2 mmol/L or non-HDL-C > 2.9 mmol/L.	Evidence from the subgroup analyses of the FOURIER trial demonstrated that treatment with evolocumab may result in added clinical benefit in patients with elevated LDL-C levels (mean LDL-C = 2.5 mmol/L, SD = 0.6) who were on a stable, optimized lipid lowering background therapy of an effective statin dose. The FOURIER trial provides limited evidence for use of evolocumab in combination with ezetimibe with approximately 3% of patients in the recent MI subgroup reporting use of ezetimibe at baseline (Gencer, et al.); however, consistent with clinical guidelines, ezetimibe is recommended as intensification of lipid-lowering therapy with or without PCSK9 inhibitors when elevated LDL-C levels are ≤ 2.2 mmol/L or equivalent.	When LDL-C cannot be measured, alternative markers (such as non-HDL-C or ApoB levels) can be used in accordance with clinical guidelines. Optimized lipid lowering background therapy was defined as treatment with an effective statin of high–to–moderate intensity (at least atorvastatin 20 mg daily or equivalent) for at least 4 weeks prior to treatment, with or without ezetimibe.
Prescribing		
3. Evolocumab should be prescribed by a cardiologist.	This is meant to ensure that evolocumab is prescribed for appropriate patients and that adverse effects are managed in an optimized and timely manner.	—
4. Evolocumab should not be reimbursed for use in combination with a PCSK9 inhibitor.	There is no evidence for the use of evolocumab in combination with a PCSK9 inhibitor.	—
Pricing		
5. A reduction in price	The ICER for evolocumab is $87,882 per QALY gained when compared with optimized background lipid lowering therapy alone. An estimated price reduction of at least 50% would be required for evolocumab to achieve an ICER of $50,000 per QALY compared to optimized background lipid lowering therapy. The estimated price reduction is associated with high uncertainty and limitations in the	—

Reimbursement condition	Reason	Implementation guidance
	economic model that could not be addressed.	
Feasibility of adoption		
6. The economic feasibility of adoption of evolocumab must be addressed	At the submitted price, the incremental budget impact of evolocumab is expected to be greater than $40 million in years 2 and 3. Further, the magnitude of uncertainty in the budget impact must be addressed to ensure the feasibility of adoption, given the difference between the sponsor's estimate and CADTH's estimate.	—

ApoB = apolipoprotein B; CV = cardiovascular; HDL-C = high-density lipoprotein cholesterol; ICER = incremental cost-effectiveness ratio; LDL-C = low-density lipoprotein cholesterol; PCSK9 = proprotein convertase subtilisin kexin type 9; QALY = quality-adjusted life year.

Discussion Points

- CDEC noted that the incremental benefit of adding evolocumab to existing therapy is small and largely limited to a reduction in MI. Death and death due to CV causes were not significantly different between groups in the overall FOURIER population. Similar results were observed for death due to CV causes in the subgroup of patients with established cardiovascular diseases (at high cardiovascular risk) considered for the reassessment of evolocumab (death by any cause was not reported in the subgroup analysis).
- The primary and key secondary endpoints for FOURIER were based on composite outcomes: the primary endpoint was time to CV death, MI, hospitalization for unstable angina, stroke, or coronary revascularization, whichever occurs first, and the key secondary endpoint was time to CV death, MI, or stroke, whichever occurs first. The results of the composite outcomes assessed in the overall FOURIER population, as well as the subgroups assessed by Gencer et al., and Sabatine et al., were similar, suggesting an incremental benefit with evolocumab compared to placebo, primarily driven by MI (as noted above).
- In the 2017 recommendation, CDEC noted a lack of evidence related to longer term outcomes beyond 26 months, the median follow-up period in the FOURIER trial, including both durability of clinical effectiveness and potential harms. The reassessment of evolocumab included an integrated analysis of two phase 3b, multi-centre, single-arm, 5-year OLE studies (FOURIER-OLE) assessing the safety, tolerability, and clinical effects of long-term evolocumab administration in patients who completed the FOURIER trial (parent trial). In support of the reimbursement request, an ad-hoc subgroup analysis of patients with prior MI was provided. Although the evidence for the subgroup of interest was considered exploratory and limited to descriptive analyses, the results observed were consistent with the treatment effect observed in the overall FOURIER-OLE, and therefore suggestive of a potential beneficial treatment effect, particularly for MI and CV death, with up to 5 years of treatment. Regarding safety, no new safety signals related to treatment with evolocumab were identified in the 5-year OLE studies of the FOURIER trial.
- The limited comparison of evolocumab to ezetimibe represents a source of uncertainty in the clinical and economic evidence. The low rate of ezetimibe use was identified as a key limitation in the original FOURIER trial as ezetimibe was used in only approximately 3% of patients in Gencer et al. 2020 subgroup analysis. CDEC acknowledged that the timing of the pivotal trial for ezetimibe and FOURIER trial is partly responsible for the limited trial evidence of evolocumab in combination with ezetimibe; however, this still represents a limitation given the change in clinical practice since 2017. Feedback from the clinical experts consulted by CADTH indicated that ezetimibe is typically the first add-on to statins when intensification of lipid-lowering therapy is indicated; however, it was noted that this is somewhat guided by requirements for reimbursement. This input aligns with the 2021 guidelines, which notes to consider ezetimibe with or without a PCSK9 inhibitor for LDL-C levels between 1.8 and 2.2 mmol/L (or ApoB 0.70 to 0.80 g/L or non-HDL-C 2.4 to 2.9 mmol/L).
- CDEC noted that at-risk populations will have different levels of risk, and the treating physician or cardiologist will need to consider these factors in determining renewal. It was noted that evolocumab reduced LDL-C by 59.9% at week 48, on average, in the Gencer et al. (2020) subgroup analysis, but this was associated with high variation.

- CDEC discussed that the economic evidence is highly uncertain due to limitations with the clinical evidence, and that CADTH was unable to resolve identified limitations through reanalysis. CDEC also noted that in the 2017 recommendation a higher price reduction was recommended. It is uncertain whether the subgroups studied in Gencer et al. demonstrate a benefit larger than the overall population studied in the FOURIER trial to justify the differing price reduction recommendation. To account for the outstanding uncertainty in the economic evidence CDEC noted that a greater price reduction than noted in Table 1 may be warranted.

Background

Hyperlipidemia refers to high levels of lipids in the blood, including cholesterol and triglycerides. High levels of cholesterol (also referred to as hypercholesterolemia), notably LDL-C, can cause atherosclerosis, defined as the buildup of fatty deposits in blood vessels leading to restriction in blood flow, which is a major cause of CV events, including heart attacks, strokes, and lower extremity and peripheral artery disease (PAD). ASCVD, as defined in the 2021 Canadian Cardiovascular Society (CCS) Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in Adults (hereafter referred to as the 2021 CCS Dyslipidemia Guidelines), comprises of all clinical conditions of atherosclerotic origin, such as acute coronary syndrome (ACS), stroke, and PAD. Following the first documented case of (index) ACS, a residual risk of subsequent CV event remains. Secondary prevention refers to the treatment and management of known, clinically evident ASCVD, and the prevention or delay of the onset of disease manifestations.

ACS is comprised of non-ST-segment elevation myocardial infarction (NSTEMI), ST-segment elevation myocardial infarction (STEMI), and unstable angina, with myocardial infarction (MI) being the most common clinical presentation. The clinical experts were consulted on the definition of ACS in relation to clinical practice. Since cardiac troponin assays have evolved to become highly sensitive to micromolar elevated levels of circulating troponin, UA has become an exceedingly infrequent diagnosis. Thus, only MI, including STEMI and NSTEMI, was considered most relevant for the purpose of this review.

The incidence rate for MI was approximately 2.5 per 1,000 person-years over the time period of 2005 to 2016 in Ontario, while the incidence rate for UA was 3.3 per 1,000 person-years in 2005 and 1.7 per 1,000 person-years in 2016. The 10-year prevalence rates for MI increased from 23.5 to 26.9 per 1,000 individuals and for UA increased from 22.1 to 23.7 per 1,000 individuals between the periods of 2004 to 2013 and 2008 to 2017.

ASCVD is a statin-indicated condition according to the 2021 CCS Dyslipidemia Guidelines. In patients with ASCVD, the guidelines advised to consider proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitors, with or without ezetimibe, when the necessary reduction in LDL-C, apolipoprotein B (ApoB), or non-high-density lipoprotein cholesterol (HDL-C) is substantial (i.e., LDL-C > 2.2 mmol/L or ApoB > 0.80 g/L or non-HDL-C > 2.9 mmol/L despite maximally tolerated statin dose) or in patients shown to derive the largest benefit from intensification of statin therapy with PCSK9 inhibitor therapy. This subset includes patients with recent ACS (i.e., hospitalized index ACS to 52 weeks post index ACS) as well as those with clinically evident ASCVD and any additional CV risk enhancers. If the necessary reduction in LDL-C, ApoB, or non-HDL-C is modest (i.e., LDL-C of 1.8 to 2.2 mmol/L or ApoB of 0.70 to 0.80 g/L or non-HDL-C 2.4 to 2.9 mmol/L despite maximally tolerated statin dose), then the guidelines advised to consider ezetimibe, with or without a PCSK9 inhibitor. According to the clinical experts consulted by CADTH for the purpose of this review, other lipid lowering therapies such as niacin, fibrates, bile acid sequestrants, mipomersen (not approved in Canada), and lomitapide (only used for homozygous familial hypercholesterolemia) are infrequently used in patients with ASCVD.

Evolocumab has been approved by Health Canada for the reduction of elevated LDL-C in adult patients with primary hyperlipidemia (including heterozygous familial hypercholesterolemia [HeFH] and ASCVD) as an adjunct to diet and statin therapy, with or without other lipid-lowering therapies, in patients who require additional lowering of LDL-C and as an adjunct to diet, alone or in combination with non-statin lipid-lowering therapies, in patients for whom a statin is contraindicated. Evolocumab is a PCSK9 inhibitor. It is available as a subcutaneous injection and the dosage recommended in the product monograph is evolocumab 140 mg every 2 weeks or 420 mg once monthly.

Submission History

Initial Submission for Primary Hyperlipidemia

In 2016, evolocumab was first reviewed by the CADTH CDEC for primary hyperlipidemia, including HeFH and clinical ASCVD. The CADTH CDEC issued a recommendation that evolocumab be listed as an adjunct to diet and maximally tolerated statin therapy in adult patients with HeFH, who require additional lowering of LDL-C, if the prespecified clinical criteria and condition are met. For the ASCVD component of the indication, the CADTH CDEC issued a recommendation that evolocumab not be listed as an adjunct to diet and maximally tolerated statin therapy in adult patients with clinical ASCVD, who require additional lowering of LDL-C. Detailed information on and reasons for the final recommendation made in 2016 by the CADTH CDEC are publicly available on the CADTH webpage.

Resubmission for the Atherosclerotic Cardiovascular Disease Component of Primary Hyperlipidemia

In 2017, evolocumab was resubmitted and reviewed by the CADTH CDEC for the ASCVD component of primary hyperlipidemia. The CADTH CDEC issued a recommendation that evolocumab be reimbursed as an adjunct to diet and maximally tolerated statin therapy in adult patients for ASCVD, who require additional lowering of LDL-C, if the prespecified criterion and condition are met. The criterion was that patients met the inclusion criteria for the FOURIER trial (i.e., established CV disease and are at high risk for future events, LDL-C ≥ 1.8 mmol/L or non-HDL-C ≥ 2.6 mmol/L, and taking maximally tolerated dose of statins). In one double-blind, placebo-controlled, randomized clinical trial enrolling patients with ASCVD receiving optimized statin therapy (FOURIER, n = 27,564), a composite outcome of CV death, MI, stroke, unstable angina, or revascularization was experienced by 9.8% of patients taking evolocumab and 11.3% of patients taking placebo over a median follow-up period of 26 months (HR = 0.85; 95% CI, 0.79 to 0.92). However, funding is not yet in place as negotiation concluded without an agreement in July 2019. Detailed information on the final recommendation made in 2017 by the CADTH CDEC is publicly available on the CADTH webpage.

Basis of Present Reassessment

The 2021 CCS Dyslipidemia Guidelines referenced the FOURIER and ODYSSEY trials that have identified subsets of patients with established CV disease (at high CV risk) who have been shown to derive the largest benefit from intensification of statin therapy with the addition of a PCSK9 inhibitor in secondary prevention. This subset includes patients with recent ACS (i.e., hospitalized index ACS to 52 weeks post index ACS) as well as those with clinically evident ASCVD and any additional CV risk enhancers, including diabetes mellitus or metabolic syndrome, polyvascular disease, symptomatic PAD, history of MI, MI in the past 2 years, previous coronary artery bypass graft surgery, an LDL-C level of 2.6 mmol/L or more or HeFH, and a lipoprotein(a) level of 60 mg/dL or more.

Hence, the focus of the present reassessment is on the revised requested reimbursement criteria: patients with recent ACS within the past 1 year, who have an LDL-C level of 1.8 mmol/L or more despite taking moderate-to-high intensity statin therapy, with or without ezetimibe.

Sources of Information Used by the Committee

To make its recommendation, the committee considered the following information:

- a review of 2 subgroup analyses of a randomized, double-blind, placebo-controlled, phase 3 clinical trial (FOURIER) and its 2 open label extension studies (FOURIER-OLE) in patients with clinically evident ASCVD and 1 randomized, double-blind, placebo-controlled study (EVOPACS) in patients with acute ACS
- no patient group input was submitted for the present reassessment
- input from public drug plans that participate in the CADTH review process
- 2 clinical specialists with expertise diagnosing and treating patients with primary hyperlipidemia
- input from 9 clinician groups, including Canadian Dyslipidemia Guideline Committee; McMaster Lipid Clinic; British Columbia Lipid Specialists; Cambridge Cardiac Rehab Program; Western University, Division of Cardiology, Cardiac Rehabilitation and Secondary Prevention Program; University of British Columbia and Vancouver General Hospital and St.

Paul's Hospital Cardiac Intensive Care Unit; University of Toronto faculty and clinicians at St Michael's Hospital; Division of Cardiology, University of Ottawa Heart Institute; and a group of primary care and specialist physicians who treat coronary artery disease and ACS across Canada

- a review of the pharmacoeconomic model and report submitted by the sponsor

Stakeholder Perspectives

The information in this section is a summary of input provided by the patient and clinician groups who responded to CADTH's call for input and from clinical experts consulted by CADTH for the purpose of this review.

Patient Input

No patient groups provided input on the present reassessment of evolocumab.

A summary of past patient input submitted by the Cardiac Health Foundation of Canada was prepared by the CADTH review team in the December 2017 CADTH Common Drug Review Report: Clinical Review Report (Resubmission) on Evolocumab (Repatha), publicly available on CADTH's webpage. The Cardiac Health Foundation of Canada is an organization that raises funds for and promotes programs and applied research on rehabilitation and management of CV disease and provides education and resources on the prevention and management of CV disease in Canada. Patient input was gathered by the patient group through an online survey (N = 55) and 1 telephone interview; respondents were patients with atherosclerosis and their caregivers.

Among the survey respondents, experience with rosuvastatin, atorvastatin, ezetimibe, and bypass surgery were described with varying degrees of effectiveness. The survey respondents reported that the most common side effects associated with their current treatment were digestive-related, including gas, constipation, and upset stomach. According to the survey respondents, the most difficult to tolerate side effects associated with current medications were muscle pain, discomfort, and weakness.

The survey respondents identified the following unmet need: alternative treatment options to statins. More specifically, in the context of elevated cholesterol levels despite a maximally tolerated statin dose and AEs commonly associated with statin therapy (i.e., loss of muscle function and muscle weakness), patients' expectation of evolocumab is to lower cholesterol levels to target levels with minimal side effects. In particular, most patients indicated that a loss of muscle function is an AE they are not willing to tolerate.

Clinician Input

Input From Clinical Experts Consulted by CADTH

The clinical experts indicated that most patients at high risk for CV events are not meeting LDL-C (or non-HDL-C or ApoB) target levels with available treatment options. Moreover, the clinical experts indicated that non-adherence due to real or perceived intolerance to high intensity statins, such as myalgias, is a challenge in clinical practice; they estimated 50% of patients discontinue their statin within 1 year after an ACS event. The clinical experts further highlighted the lack of access to advanced therapies, including PCSK9 inhibitors, experienced by patients with ASCVD.

The clinical experts referenced the 2021 CCS Dyslipidemia Guidelines, indicating that ezetimibe and PCSK9 inhibitors are second-line treatment options in the management of primary hyperlipidemia for secondary prevention. More specifically, the clinical experts indicated that ezetimibe and/or evolocumab would be used in addition to a maximally tolerated statin dose to meet LDL-C (or non-HDL-C or ApoB) target levels. For patients who are intolerant of or have contraindications to statins, the clinical experts indicated that evolocumab would be an alternative therapy to statins, with or without ezetimibe.

The clinical experts referenced the 2021 CCS Dyslipidemia Guidelines to identify the patient population most in need of an intervention for the management of primary hyperlipidemia in secondary prevention – the subset of patients with ASCVD (at high CV risk) who have been shown to derive the largest benefit from intensification of statin therapy with the addition of a PCSK9 inhibitor. This includes patients with recent ACS, defined as hospitalized index ACS to 52 weeks post index ACS, and patients with additional CV risk enhancers. Additionally, the clinical experts indicated that all patients with ASCVD whose LDL-C (or non-HDL-C or ApoB) remains above threshold despite a maximally tolerated statin dose are suited for treatment with evolocumab.

The clinical experts indicated that although a specialist would not be required to diagnose, treat, and monitor patients who would receive evolocumab, this should ideally be carried out in an outpatient clinic or hospital by a clinician who has experience with evolocumab. The clinical experts referenced the LDL-C, non-HDL-C, and ApoB thresholds in the 2021 CCS Dyslipidemia Guidelines as the treatment goal. According to the clinical experts, treatment response is based on the reduction in LDL-C (or non-HDL-C or ApoB) levels that is assessed every 6 to 12 months in practice, depending on CV risk. When deciding to discontinue treatment with evolocumab, the clinicals experts would consider the side effects associated with treatment and competing risk from other disease with limited life expectancy.

Clinician Group Input

A total of 9 clinician groups provided their input on the present reassessment of evolocumab: Canadian Dyslipidemia Guideline Committee; McMaster Lipid Clinic; British Columbia Lipid Specialists; Cambridge Cardiac Rehab Program; Western University, Division of Cardiology, Cardiac Rehabilitation and Secondary Prevention Program; University of British Columbia and Vancouver General Hospital and St. Paul's Hospital Cardiac Intensive Care Unit; University of Toronto faculty and clinicians at St Michael's Hospital; Division of Cardiology, University of Ottawa Heart Institute; and a group of primary care and specialist physicians who treat coronary artery disease and ACS across Canada.

The clinician groups identified the following limitations with currently available treatments (unmet needs) in patients with recent ACS: limited access to PCSK9 inhibitors due to cost, experience of side effects and/or intolerance to available drugs (which have an impact on adherence to treatment), and variable treatment response (e.g., treatment targets for LDL-C not met). The University of Ottawa Heart Institute highlighted that although the majority of patients with ASCVD experience a reduction in their LDL-C level to below 1.8 mmol/L using high dose statin therapy, with or without ezetimibe, a subset of patients continues to have elevated lipid levels due to severe polygenic hypercholesterolemia and intolerance or contraindication to high dose statin therapy. The clinician group further suggested that this subset of patients who are at high risk of recurrent CV events would benefit from additional lipid lowering treatment in the form of a PCSK9 inhibitor.

The Canadian Dyslipidemia Guideline Committee, McMaster Lipid Clinic, and the group of primary care and specialist physicians across Canada referenced the 2021 CCS Dyslipidemia Guidelines to indicate that a PCSK9 inhibitor would be used as an add-on therapy after initiating maximally tolerated statin therapy, with or without ezetimibe, in patients with elevated LDL-C levels. More specifically, evolocumab would be used in second line after a maximally tolerated dose of statin or in third line after statin and ezetimibe. The Canadian Dyslipidemia Guideline Committee also referenced the guidelines to identify candidates for evolocumab, comprising of patients with either a recent ACS (i.e., within 52 weeks of hospitalization) or prior ASCVD with any of the following: diabetes or metabolic syndrome, polyvascular disease, symptomatic PAD, recurrent MI, MI in the past 2 years, previous coronary artery bypass graft surgery, LDL-C level of 2.6 mmol/L or more, or HeFH. The clinician groups indicated that treatment response is assessed based on the percent reduction in LDL-C (or non-HDL-C or ApoB) levels, compared to pre-treatment levels in practice.

Drug Program Input

Input was obtained from the drug programs that participate in the CADTH reimbursement review process. The following were identified as key factors that could potentially impact the implementation of a CADTH recommendation for evolocumab:

- Relevant comparators
- Consideration for initiation of therapy
- Consideration for continuation or renewal of therapy
- Consideration for prescribing of therapy
- System and economic issues

The clinical experts consulted by CADTH provided advice on the potential implementation issues raised by the drug programs.

Table 2. Responses to Questions from the Drug Programs

Implementation issues	Response
Considerations for initiation of therapy	
In patients who are taking evolocumab and experience waning of effect, can they be switched to another monoclonal antibody (e.g., alirocumab) or inclisiran?	The clinical experts considered this to be an unlikely scenario – waning of effect with PCSK9 inhibitors is typically not expected and there are barriers to access to alirocumab and inclisiran (i.e., these drugs are currently not reimbursed by the public drug plans for the indication under review). The clinical experts indicated that it would be reasonable to consider switching from treatment with evolocumab to another monoclonal antibody or inclisiran if a patient taking evolocumab experiences waning of effect; however, there is a no evidence for switching therapies. CDEC defers to the expertise of the clinical experts.
Should evolocumab only be used in combination therapy with maximally tolerated statin dose and ezetimibe?	The clinical experts indicated that evolocumab would be used in addition to a maximally tolerated statin dose, with or without ezetimibe. For patients who are intolerant or have contraindications to statins, the clinical experts indicated that evolocumab would be an alternative therapy to statins, with or without ezetimibe. The clinical experts advised to refer to the 2021 CCS Dyslipidemia Guidelines for additional context on the place in therapy of evolocumab in relation to ezetimibe. The guidelines advised to consider a PCSK9 inhibitor, with or without ezetimibe, when the necessary reduction in LDL-C, ApoB, or non-HDL-C is substantial[a] or in patients shown to derive the largest benefit from intensification of statin therapy with the additional use of a PCSK9 inhibitor. This subset includes patients with recent ACS[b] as well as those with clinically evident ASCVD and any additional cardiovascular risk enhancers[c]. If the necessary reduction in LDL-C, ApoB, or non-HDL-C is modest[d], then the guidelines advised to consider ezetimibe, with or without a PCSK9 inhibitor. CDEC agrees with the clinical experts on the use of evolocumab in combination with maximally tolerated statin dose, as per the 2021 CCS Dyslipidemia Guidelines. Although the submitted evidence was suggestive of a larger benefit for patients with a recent ACS, CDEC noted that statistical analyses strongly suggest that chance cannot be excluded as a likely explanation. The clinical experts noted to CDEC that any reduction of LDL-C is associated with potential benefits and ezetimibe in combination with statins is associated with an approximately 20% reduction in LDL-C, on average. For this reason, CDEC recommends that evolocumab be considered after an adequate trial of ezetimibe for patients with an LDL-C between 1.8 and 2.2 mmol/L. Where there are gaps in the submitted evidence, CDEC defers to the expertise of the clinical experts on the use of evolocumab in combination with ezetimibe.
Considerations for continuation or renewal of therapy	
For currently listed evolocumab, requests have been received from prescribers in the context of an elevated	The clinical experts agreed with using non-HDL-C (< 2.4 mmol/L) and ApoB (< 0.7 g/L) levels as alternative markers to assess

Implementation issues	Response
triglyceride level and as a result, LDL-C could not be calculated. If LDL-C cannot be obtained due to an elevated triglyceride level, is there an alternative marker(s) that can be used to assess the appropriateness of therapy (e.g., non-HDL level < 2.4 mmol/L or ApoB < 0.7 g/L)? Is ApoB measurement accessible and considered in routine blood work in practice?	appropriateness of therapy with evolocumab in the setting of an elevated triglyceride level. The clinical experts noted that ApoB is a separate test that is publicly reimbursed by all provinces in Canada, while the non-HDL-C is available in a standard lipid panel. The CADTH review team notes that the 2021 CCS Dyslipidemia Guidelines advise on the use of non-HDL-C or ApoB in place of LDL-C as the preferred lipid parameter for screening in patients with elevated triglyceride (> 1.5 mmol/L). CDEC agrees with the clinical experts.
Considerations for prescribing of therapy	
What is the maximum dose of evolocumab for reimbursement?	The CADTH review team notes that the recommended dose of evolocumab SC for the indication under review is 140 mg every 2 weeks or 420 mg once monthly. This aligns with the dose schedules of intervention that were available to patients for selection in the FOURIER trial. The CADTH review team also notes that the product monograph comments on switching between dose schedules. This aligns with the FOURIER trial in which dose adjustments were not permitted, with the exception of switching between dose schedules per patient preference. CDEC agrees with the clinical experts.
Is there evidence that evinacumab or inclisiran can be used in combination to augment the effect of evolocumab?	The clinical experts indicated that evinacumab is approved by Health Canada for HoFH and as such, would not generally be used for the indication under review. Regarding inclisiran, the clinical experts indicated that it would not be appropriate to combine drugs with the same mechanism of action and that there is no evidence on combining with a PCSK9 inhibitor. CDEC defers to the expertise of the clinical experts.
Relevant comparators	
In the FOURIER trial, the comparator was matching placebo injection, and an inclusion criterion was to be on a stable, optimized lipid lowering background therapy consisting of an effective statin dose (i.e., high-to-moderate intensity statin), with or without ezetimibe. Statins and ezetimibe are open benefits.	Comment from the drug programs to inform CDEC deliberations. The clinical experts indicated that statins, ezetimibe, and PCSK9 inhibitors are relevant comparators for this review. Regarding PCSK9 inhibitors, the CADTH review team notes that funding is not yet in place for alirocumab as negotiation concluded without an agreement in October 2019 for the indication of ASCVD. CDEC defers to the expertise of the clinical experts.
Considerations for initiation of therapy	
Calculated LDL-C is accessible and considered in routine blood work in practice.	Comment from the drug programs to inform CDEC deliberations.
Evolocumab is currently listed as limited use benefit for heterozygous familial hypercholesterolemia who require additional lowering of LDL-C.	Comment from the drug programs to inform CDEC deliberations.

Implementation issues	Response
Considerations for continuation or renewal of therapy	
Consistency in renewal criteria with currently listed evolocumab and any other drugs reviewed by CADTH in the same therapeutic space (e.g., alirocumab and inclisiran) is preferred.	Comment from the drug programs to inform CDEC deliberations. The clinical experts advised on using a reduction in LDL-C (or non-HDL-C or ApoB) to assess treatment response every 6 to 12 months, depending on the patient's cardiovascular risk. The clinical experts advised that the treatment goal in patients with ASCVD who are at high cardiovascular risk is to reduce the levels to below thresholds referenced in the 2021 CCS Dyslipidemia Guidelines (i.e., LDL-C < 1.8 mmol/L or non-HDL-C < 2.4 mmol/L or ApoB < 0.7 g/L). CDEC referred to the 2021 CCS Dyslipidemia Guidelines which noted that to date, no clear target for reduction in LDL-C (or non-HDL-C or ApoB) levels has been identified in RCTs. Instead, such trials have generally used thresholds of LDL-C (or non-HDL-C or ApoB) levels for initiation or intensification of lipid-lowering therapies. CDEC also highlighted that the at-risk population will present with varying levels of risk, which the cardiologist will need to take into consideration when determining renewal. CDEC suggested that if a patient continues to present with LDL-C (or non-HDL-C or ApoB) levels above thresholds referenced in the 2021 CCS Dyslipidemia Guidelines, then renewal should be allowed.
Considerations for prescribing of therapy	
Evolocumab can be administered at home with an autoinjector.	Comment from the drug programs to inform CDEC deliberations.
There are no limitations on the prescriber requirements for currently listed evolocumab (e.g., the prescriber is not required to be a cardiologist or in internal medicine).	Comment from the drug programs to inform CDEC deliberations. The clinical experts indicated that although a specialist is not required for the diagnosis, treatment, and monitoring of patients receiving evolocumab, this should ideally be carried out by a clinician who has experience with evolocumab. CDEC defers to the expertise of the clinical experts. Although consensus guidelines exist for the management of dyslipidemia, different patterns of practice and interpretations of the clinical evidence were apparent in the input from cardiologist groups. CDEC discussed that prescribing decisions likely require the expertise of cardiologists to interpret and implement the guidelines related to evolocumab.
System and economic issues	
Based on the budget impact analysis, there is a large potential budget impact considering ACS is a common condition.	Comment from the drug programs to inform CDEC deliberations.

ApoB = apolipoprotein B; ASCVD = atherosclerotic cardiovascular disease; CCS = Canadian Cardiovascular Society; CDEC = Canadian Drug Expert Committee; HDL-C = high-density lipoprotein cholesterol; HoFH = homozygous familial hyperlipidemia; LDL-C = low-density lipoprotein cholesterol; PCSK9 = proprotein convertase subtilisin kexin type 9; RCT = randomized controlled trials; SC = subcutaneous.

[a] Substantial refers to LDL-C greater than 2.2 mmol/L or ApoB greater than 0.80 g/L or non-HDL-C greater than 2.9 mmol/L despite a maximally tolerated statin dose.

[b] Recent ACS is defined in the guidelines as hospitalized index ACS to 52 weeks post index ACS.

[c] Cardiovascular risk enhancers, according to the guidelines, include diabetes mellitus or metabolic syndrome, polyvascular disease, symptomatic PAD, history of MI, MI in the past 2 years, previous coronary artery bypass graft surgery, an LDL-C level of 2.6 mmol/L or more or HeFH, and a lipoprotein(a) level of 60 mg/dL or more.

[d] Modest refers to LDL-C of 1.8 to 2.2 mmol/L or ApoB of 0.70 to 0.80 g/L or non-HDL-C 2.4 to 2.9 mmol/L despite a maximally tolerated statin dose.

Clinical Evidence

Systematic Review

Description of Studies

The FOURIER trial was a phase 3, double-blind, placebo-controlled, randomized clinical trial (N = 27,564). The primary objective was to evaluate the effect of evolocumab, compared to placebo, on the risk of CV death, MI, stroke, hospitalization for unstable angina, or coronary revascularization, whichever occurs first, in patients with clinically evident ASCVD. The trial included patients with LDL-C of 1.8 mmol/L or more (or a non-HDL-C of 2.6 mmol/L or more) after at least 2 weeks of optimized statin therapy, with or without ezetimibe. Patients were randomized in a 1:1 ratio to receive either subcutaneous evolocumab (140 mg once every 2 weeks or 420 mg once every month, per patient preference) or matching placebo injection. Randomization was stratified by the final screening LDL-C level and geographical region. Treatment continued until a minimum of 1,630 patients experienced an event adjudicated by an independent external Clinical Events Committee (CEC) as qualifying for a key secondary end point event of CV death, MI, or stroke. The estimated study duration was 56 months from the date the first patient was randomized.

The Gencer et al. and Sabatine et al. (2018) studies were subgroup analyses of the FOURIER trial. The objective of the Gencer et al. study was to evaluate the risks of major adverse CV events as a function of time from the date of the qualifying MI and evaluate the effect of evolocumab on CV outcomes in patients with a MI within 1 year. The objective of the Sabatine et al. (2018) study was to assess the efficacy of evolocumab in 3 subgroups in the FOURIER trial: timing from the most recent MI, number of prior MIs, and the presence of residual multivessel coronary artery disease. The subgroup of patients with prior MI within 1 year from the Gencer et al. study and the subgroup of patients with prior MI within 2 years in the Sabatine et al. (2018) study were considered most relevant for the purpose of this review. Outcomes on clinical events (CV death, MI, stroke, hospitalization for unstable angina, or coronary revascularization) were assessed after a median follow-up of 26 months and LDL-C (LDL < 1.8 mmol/L and change from baseline) was also assessed at weeks 4 and 48.

In the Gencer et al. study, a total of 2,821 patients were randomized to receive evolocumab and 2,890 patients were randomized to receive placebo, according to the subgroup of patients with prior MI within 1 year. The mean age of patients was 59.7 years (standard deviation [SD] = 9.3 years) in the evolocumab group and 59.5 years (SD = 9.2 years) in the placebo group. The mean time from MI to enrollment was 5.379 months (SD = 2.965 months) in the evolocumab group and 5.355 months (SD = 2.911 months) in the placebo group. Almost all patients had at least 1 major CV risk factor or at least 2 minor CV risk factors (99.8% [n = 2,814] of patients in the evolocumab group and 99.8% [n = 2,884] of patients in the placebo group). At baseline, the mean LDL-C was 2.453 mmol/L (SD = 0.647 mmol/L) in the evolocumab group and 2.467 mmol/L (SD = 0.647 mmol/L) in the placebo group. Almost all patients were taking a statin at baseline, with 99.9% of patients (n = 2,819) in the evolocumab group and 100.0% of patients (n = 2,889) in the placebo group. A total of 3.2% of patients (n = 91) in the evolocumab group and 3.3% of patients (n = 95) in the placebo group were taking ezetimibe at baseline.

In general, the baseline characteristics of patients with prior MI within 2 years in the Sabatine et al. (2018) study were similar to the baseline characteristics of those with prior MI within 1 year in the Gencer et al. study. A total of 4,109 patients were randomized to receive evolocumab and 4,293 patients were randomized to receive placebo, according to the subgroup of patients with prior MI within 2 years. The mean time from MI to enrollment was 9.191 months (SD = 6.441 months) in the evolocumab group and 9.366 months (SD = 6.544 months) in the placebo group.

Efficacy Results

Cardiovascular death, myocardial infarction, or stroke

Of the patients with a prior MI within 1 year, this composite end point was experienced by 6.45% (n = 182) of patients taking evolocumab versus 8.58% (n = 248) of patients taking placebo (HR = 0.75; 95% CI, 0.62 to 0.91). Of the patients with a prior MI in 1

year or more, this composite end point was experienced by 6.04% (n = 502) of patients taking evolocumab versus 7.04% (n = 584) of patients taking placebo (HR = 0.85; 95% CI, 0.76 to 0.96).

Of the patients with a prior MI within 2 years, this composite end point was experienced by 6.45% (n = 265) of patients taking evolocumab versus 8.43% (n = 362) of patients taking placebo (HR = 0.76; 95% CI, 0.64 to 0.89). Of the patients with a prior MI in 2 years or more, this composite end point was experienced by 5.97% (n = 419) of patients taking evolocumab versus 6.81% (n = 470) of patients taking placebo (HR = 0.87; 95% CI, 0.76 to 0.99).

Cardiovascular death

Of the patients with a prior MI within 1 year, this mortality end point was experienced by 1.77% (n = 50) of patients taking evolocumab versus 1.80% (n = 52) of patients taking placebo (HR = 1.00; 95% CI, 0.68 to 1.47). Of the patients with a prior MI in 1 year or more, this end point was experienced by 1.88% (n = 156) of patients taking evolocumab versus 1.64% (n = 136) of patients taking placebo (HR = 1.15; 95% CI, 0.91 to 1.44).

This mortality end point was not assessed in patients according to the subgroup by prior MI within 2 years versus 2 years or more.

Myocardial infarction (fatal or non-fatal)

Of the patients with a prior MI within 1 year, this CV end point was experienced by 4.50% (n = 127) of patients taking evolocumab versus 6.61% (n = 191) of patients taking placebo (HR = 0.67; 95% CI, 0.54 to 0.84). Of the patients with a prior MI in 1 year or more, this CV end point was experienced by 3.56% (n = 296) of patients taking evolocumab versus 4.57% (n = 379) of patients taking placebo (HR = 0.78; 95% CI, 0.67 to 0.91).

This CV end point was not assessed in patients according to the subgroup by prior MI within 2 years versus 2 years or more.

Stroke (fatal or non-fatal)

Of the patients with a prior MI within 1 year, this cerebrovascular end point was experienced by 1.06% (n = 30) of patients taking evolocumab versus 1.31% (n = 38) of patients taking placebo (HR = 0.81; 95% CI, 0.50 to 1.31). Of the patients with a prior MI in 1 year or more, this cerebrovascular end point was experienced by 1.32% (n = 110) of patients taking evolocumab versus 1.65% (n = 137) of patients taking placebo (HR = 0.80; 95% CI, 0.62 to 1.03).

This cerebrovascular end point was not assessed in patients according to the subgroup by prior MI within 2 years versus 2 years or more.

Cardiovascular death, myocardial infarction, hospitalization for unstable angina, stroke, or coronary revascularization

Of the patients with a prior MI within 1 year, this composite end point was experienced by 11.45% (n = 323) of patients taking evolocumab versus 14.12% (n = 408) of patients taking placebo (HR = 0.81; 95% CI, 0.70 to 0.93). Of the patients with a prior MI in 1 year or more, this composite end point was experienced by 10.24% (n = 851) of patients taking evolocumab versus 11.10% (n = 921) of patients taking placebo (HR = 0.92; 95% CI, 0.84 to 1.01).

Of the patients with a prior MI within 2 years, this composite end point was experienced by 11.17% (n = 459) of patients taking evolocumab versus 13.72% (n = 589) of patients taking placebo (HR = 0.80; 95% CI, 0.71 to 0.91). Of the patients with a prior MI in 2 years or more, this composite end point was experienced by 10.19% (n = 715) of patients taking evolocumab versus 10.73% (n = 740) of patients taking placebo (HR = 0.95; 95% CI, 0.85 to 1.05).

Change from baseline in low-density lipoprotein cholesterol

Of the patients with a prior MI within 1 year, the mean LDL-C was 2.453 mmol/L (SD = 0.647 mmol/L) in the evolocumab group and 2.467 mmol/L (SD = 0.647 mmol/L) in the placebo group at baseline. Patients with a prior MI within 1 year experienced a mean percent change from baseline in LDL-C of –59.90% (SD = 30.12%) in the evolocumab group and 2.00% (SD = 27.41%) in the placebo group at week 48. Of the patients with a prior MI in 1 year or more, the mean LDL-C was 2.563 mmol/L (SD = 0.784 mmol/L) in the evolocumab group and 2.545 mmol/L (SD = 0.711 mmol/L) in the placebo group at baseline. Patients with a prior MI in 1 year

or more experienced a mean percent change from baseline in LDL-C of –60.60% (SD = 30.53%) in the evolocumab group and –0.98% (SD = 25.70%) in the placebo group at week 48.

Of the patients with a prior MI within 2 years, the mean LDL-C was 2.476 mmol/L (SD = 0.670 mmol/L) in the evolocumab group and 2.472 mmol/L (SD = 0.639 mmol/L) in the placebo group at baseline. Patients with a prior MI within 2 years experienced a mean percent change from baseline in LDL-C of –59.61% (SD = 31.05%) in the evolocumab group and 1.28% (SD = 26.73%) in the placebo group at week 48. Of the patients with a prior MI in 2 years or more, the mean LDL-C was 2.570 mmol/L (SD = 0.796 mmol/L) in the evolocumab group and 2.557 mmol/L (SD = 0.727 mmol/L) in the placebo group at baseline. Patients with a prior MI in 2 years or more experienced a mean percent change from baseline in LDL-C of –60.90% (SD = 30.05%) in the evolocumab group and –1.14% (SD = 25.79%) in the placebo group at week 48.

Harms Results

Safety outcomes were not assessed by subgroups.

Treatment Emergent Adverse Events

The proportions of patients with at least 1 TEAE or at least 1 serious adverse event (SAE) were similar between treatment groups. A total of 10,664 patients (77.4%) in the evolocumab group and 10,644 patients (77.4%) in the placebo group reported at least 1 TEAE, with the most common TEAE being diabetes mellitus which was reported in 1,207 patients (8.8%) and 1,130 patients (8.2%), respectively. A total of 3,410 patients (24.8%) in the evolocumab group and 3,404 patients (24.7%) in the placebo group reported at least 1 SAE, with the most common SAE being UA which was reported in 233 patients (1.7%) and 278 (2.0%), respectively.

The proportions of patients who stopped treatment due to any TEAE were also similar between treatment groups. A total of 608 patients (4.4%) in the evolocumab group and 573 patients (4.2%) in the placebo group stopped treatment due to any TEAE, with the most common TEAE being myalgia which was reported in 37 patients (0.3%) and 46 patients (0.3%), respectively.

Treatment Emergent Adverse Events of Special Interest

The proportions of patients with TEAEs of special interest, including potential hypersensitivity, injection site reaction, muscle, neurocognitive, demyelination and peripheral neuropathy, hepatitis C infection, and transaminase elevations and hepatic disorder events, were similar between treatment groups. A total of 13 patients (< 0.1%) in the evolocumab group and 15 patients (0.1%) in the placebo group had a potential muscle-related AE (according to a narrow search strategy included rhabdomyolysis, myopathy, and myoglobin blood increased). A total of 1,381 patients (10.0%) in the evolocumab group and 1,344 patients (9.8%) in the placebo group had a potential muscle-related AE (according to a broader search strategy).

Critical Appraisal

Internal Validity

The Gencer et al. and Sabatine et al. (2018) studies were based on subgroup analyses of the FOURIER trial. The subgroup analyses were based on the statistical methods from the FOURIER trial and the subgroups by timing of prior MI were prespecified; however, there was no clear hypothesis stated a priori. The P values on test for interaction term (in general, greater than 0.05, with the exception of the primary end point in the subgroup analysis by timing of prior MI < 2 years versus ≥ 2 years) strongly suggest that chance cannot be excluded as a likely explanation for the differential subgroup effect. There is a lack of evidence from randomized controlled trials and large observational studies to support consistent and similar findings from the subgroup analyses. Nonetheless, the subgroup analyses results were generally consistent with the overall FOURIER trial results, with the exception of stroke for which the HR was 0.79 (95% CI, 0.66 to 0.95), while the corresponding subgroup analysis results included null values.

Sample size calculation was based on the key secondary endpoint of the full analysis set in the FOURIER trial, but not for the subgroup analyses. Consequently, there is an increased likelihood of producing unreliable or inaccurate results and in particular, on CV death and stroke, components of the composite endpoints for which the 95% CI results included null values. Nonetheless, the sample size of subgroups was considered relatively large. Multiplicity was not accounted for in the subgroup analyses; therefore, the interpretation of the subgroup analysis results is subject to an increased likelihood of type I error.

In consideration of the above conditions that can lower the credibility and reliability of the subgroup analysis results, the available evidence should not be viewed as conclusive; however, they may be interpreted as likely indicative of a possible subgroup effect.

External Validity

In consideration of the sponsor's reimbursement request focused on patients with recent ACS within the past 1 year, the clinical experts were consulted on the patient population included in the subgroup analyses, which did not include patients with UA and recent (within 4 weeks) MI or stroke. Though evidence in these patients is lacking, the experts did not identify any major concerns with generalizing the subgroup analysis results to these patients.

Overall, no key concerns were identified for the generalizability of the subgroup analysis results to the patient population in the reimbursement request. Of note, the estimated study duration was 56 months from the date the first patient was randomized; however, the median follow-up was 26 months. In the previous review of the FOURIER trial by CADTH, the length of follow-up was deemed likely too short to assess the long-term harms associated with the use of evolocumab.

Long-Term Extension Studies

Description of Studies

Patients who completed the FOURIER trial had the option to enroll in one of the two 5-year extension studies (one study was conducted in North America and Eastern Europe and the other study was conducted in Western Europe) with open-label evolocumab (N = 5,305 and N = 1,600, respectively). The primary objective of both studies was to describe the safety and tolerability of long-term administration of evolocumab. An ad-hoc subgroup analysis of the OLE studies was also conducted in the subset of patients who experienced an MI before or during the parent trial. Comparisons were made between patients randomized to receive evolocumab versus placebo in the parent trial. All results reported herein are the integrated data from the 2 OLE studies.

The mean age of patients in the MI subgroup was 62.2 years (SD = 8.7 years) in the evolocumab group and 62.0 years (SD = 8.6 years) in the placebo group. Most of the participants were male in this subgroup (79.3% in the evolocumab group and 78.8% in the placebo group). At baseline, the mean LDL-C for the MI subgroup was 2.5 mmol/L (SD = 0.7 mmol/L) in both evolocumab and placebo groups. These characteristics were similar in the overall FOURIER-OLE study population as well. Time since most recent MI for the MI subgroup was 8.070 years (SD = 6.137 years) in the evolocumab group and 7.835 years (SD = 5.905 years) in the placebo group.

For the overall FOURIER-OLE study population, the mean time from MI to enrollment was 69.606 months (SD = 74.237 months) in the evolocumab group and 68.531 months (SD = 71.613 months) in the placebo group. Most of the participants were white (93.4% in the evolocumab group and 94.5% in the placebo group). The major and minor CV risk factors, as well as risk factor counts, were similar between the evolocumab and placebo groups for the overall OLE population. These baseline characteristics were not available for the MI subgroup population.

Efficacy Results

Change From Baseline in LDL-C

Among patients in the FOURIER-OLE studies, the median baseline reflexive LDL-C in the parent trial was 2.36 mmol/L (Q1 and Q3 = 2.06 and 2.80 mmol/L); the baseline LDL-C level was similar between patients in the 2 randomized treatment groups from the parent trial. The observed mean percent reduction from baseline in LDL-C ranged from 53.4% to 67.2% during the 260-week OLE study period.

In the subset of patients (n = 5582) with an MI prior to and/or during the parent FOURIER trial, the mean baseline LDL-C in the parent trial was 2.52 mmol/L (SD = 0.695 mmol/L), which was similar between patients randomized to receive evolocumab versus placebo in the parent trial. The mean LDL-C at the 260-week OLE study period for the MI subgroup of patients was 1.061 mmol/L (SD = 0.924 mmol/L). The mean percent reduction from baseline in LDL-C was approximately 57.7% at week 260 and was similar between patients who received evolocumab versus placebo in the parent trial.

Time To Major Cardiovascular Events

During the OLE study period, 490 (14.6%) patients originally randomized to the evolocumab group in the parent study experienced the FOURIER primary outcome of CV death, MI, stroke, hospitalization for unstable angina, or coronary revascularization, compared to 551 (16.8%) patients originally randomized to the placebo group (HR = 0.85; 95% CI, 0.75 to 0.96). The HR for the key secondary composite outcome of CV death, MI, or stroke was 0.80 (95% CI, 0.68 to 0.93). Of note, the HR for the individual component of CV death was 0.77 (95% CI, 0.60 to 0.99).

Among patients who had an MI prior to and/or during the parent FOURIER trial, 406 (14.42%) patients who were randomized to receive evolocumab in the parent trial experienced the FOURIER primary outcome of CV death, MI, stroke, hospitalization for unstable angina, or coronary revascularization, compared with 478 (17.28%) patients who were randomized to receive placebo in the parent trial (HR = 0.81; 95% CI, 0.71 to 0.93). The HR for the key secondary composite outcome of CV death, MI, or stroke was 0.77 (95% CI, 0.65 to 0.90); of note, the HR for the individual component of CV death was 0.68 (95% CI, 0.51 to 0.91). Event probabilities and, consequently, the difference in event probabilities between treatment groups from the parent trial were not available for the MI subgroup analysis.

Harms Results

In the integrated OLE safety analysis set, 2894 (86.3%) patients randomized to evolocumab in the parent study and 2830 (86.4%) patients randomized to placebo experienced at least one adverse event during the OLE studies. The most frequently reported AE was hypertension (15% of evolocumab-treated and 14.6% of placebo-treated patients). Other AEs reported by at least 5% of patients in either parent study treatment group include nasopharyngitis, bronchitis, arthralgia, diabetes mellitus, atrial fibrillation, back pain, upper respiratory tract infection, angina pectoris, and pneumonia.

Approximately 43% of patients experienced at least one SAE during the OLE studies (43.4% in patients randomized to the evolocumab group in the parent study and 42.7% in patients randomized to placebo). Acute MI, angina pectoris, pneumonia, atrial fibrillation, and cardiac failure were among those reported most frequently (in 2% to 3% of patients).

Overall, approximately 8% of patients experienced an AE leading to discontinuation of evolocumab during the OLE study (7.7% of patients who received evolocumab in the parent study and 8.0% of patients who received placebo in the parent study). The most frequently reported AEs leading to discontinuation of evolocumab in the OLE studies were in the system organ class of neoplasms, benign, malignant and unspecified (including cysts and polyps) (2.0% to 2.1% of patients), followed by cardiac disorders (1.5% to 2.1% of patients). None of the reported AEs leading to discontinuation were reported in more than 1% of patients. The most commonly reported fatal adverse events were in the system organ class of cardiac disorders; neoplasms benign, malignant and unspecified (including cysts and polyps) and infections and infestations.

Notable harms reported by at least 1% of patients in any treatment group in the OLE safety analysis set included potential injection site reaction events, potential demyelination events (peripheral neuropathy, sensory abnormalities not elsewhere classifiable, and chronic polyneuropathies), and transaminase elevations and potential hepatic disorders (liver function analyses and Hepatocellular damage and hepatitis not elsewhere classifiable). The numbers were similar in the evolocumab and placebo groups.

The evolocumab safety profile of the MI subgroup was similar to that seen in the overall study population.

Critical Appraisal

Internal Validity

An open-label study design can influence the perception of improvement and/or harms by patients and clinicians; in particular, in outcomes that are subjective in measurement and interpretation. However, since all fatal or non-fatal CV events or deaths were adjudicated by an external independent CEC, the assessment of the primary and key secondary end points in the FOURIER-OLE studies were not likely to have been affected by the open-label design.

In consideration of the descriptive analyses used in the OLE studies and the ad-hoc subgroup analysis of patients with prior MI, the available evidence should only be considered suggestive of a potential treatment effect, subject to uncertainty associated with the exploratory nature of the analyses.

External Validity

The baseline characteristics of all patients enrolled in the FOURIER-OLE studies were similar between the randomized treatment groups from the parent FOURIER trial. Although most patients were from the study sites located in Europe (> 66%), their demographics were generally similar to the patient population in Canada. In general, the baseline characteristics of patients in the MI subgroup were similar to the overall OLE patient population.

In consideration of the sponsor's reimbursement request that is focused on the patient population with recent ACS within the past 1 year, it should be noted that the MI subgroup included patients who had a MI prior to and/or during the parent FOURIER trial. The mean time from the most recent MI to enrollment in the overall OLE patient population was 69.606 months (SD = 74.237 months) in patients who were randomized to evolocumab in the parent trial and 68.531 months (SD = 71.613 months) in patients who were randomized to placebo in the parent trial. In the subset of patients with prior MI, the mean time from the most recent MI was 8.070 years (SD = 6.137 years) in patients who were randomized to evolocumab in the parent trial and 7.835 years (SD = 5.905 years) in patients who were randomized to placebo in the parent trial.

Indirect Comparisons

No evidence on indirect treatment comparisons were submitted by the sponsor.

Study Addressing Gap in the Evidence From the Systematic Review

Description of Study

The EVOPACS study was a phase 3, double-blind, placebo-controlled, randomized trial (N = 308). The primary objective was to assess the effectiveness of evolocumab 420 mg once every month, compared to placebo, in the reduction of LDL-C at week 8 in patients receiving high-intensity statin treatment during the acute phase of ACS.

The mean age of patients was 60.5 years (SD = 12.0 years) in the evolocumab group and 61.0 years (SD = 10.7 years) in the placebo group. Most of the participants were male (83% in the evolocumab group and 80% in the placebo group). While half of the patients in both groups had history of smoking, the active smokers were higher in the evolocumab group (41%) compared to the placebo group (30%). Most of the enrolled patients in this study were statin-naïve (80% in the evolocumab group and 76% in the placebo group). In terms of Index ACS events, 57% in the evolocumab group and 70% in the placebo group had NSTE-ACS, and 43% in the evolocumab group and 30% in the placebo group had STEMI.

Efficacy Results

The mean change from baseline in LDL-C was –77.1% (SD = 15.8%) in the evolocumab group versus –35.4% (SD = 26.6%) in the placebo group at week 8 (least squares mean difference = –40.7%; 95% CI, –45.2% to –36.2%). The mean LDL-C level at week 8 was 0.79 mmol/L (SD = 0.46 mmol/L) in the evolocumab group and 2.06 mmol/L (SD = 0.63 mmol/L) in the placebo group. At week 8, the proportion of patients with LDL-C levels of less than 1.8 mmol/L was 95.7% of patients in the evolocumab group compared to 37.6% in the placebo group.

Harms Results

A total of 78 (50%) patients in the evolocumab group and 77 (51%) patients in the placebo group experienced at least 1 adverse event during the study. Nonserious adverse events, including prespecified adverse event categories, occurred in 73 (47%) evolocumab patients and 71 (47%) placebo patients; for 2 (1.3%) patients (both in the placebo group), these adverse events led to discontinuation of investigational product. The most common adverse event was chest pain (8 [5.2%] evolocumab; 8 [5.3%] placebo), followed by musculoskeletal pain (10 [6.5%] evolocumab; 5 [3.3%] placebo), and nasopharyngitis (7 [4.5%] evolocumab; 4 [2.6%] placebo).

Serious adverse events occurred in 12 (7.7%) patients in the evolocumab group and 11 (7.2%) patients in the placebo group with 3 (1.0%) patients (2 [1.3%] evolocumab, 1 [0.7%] placebo) experiencing serious adverse events leading to discontinuation of investigational product. Two patients (both in the evolocumab group) died during the study; neither death was considered related to investigational product by the investigator or the Data Safety and Monitoring Board and both were adjudicated as CV death.

Key Takeaways

Interpretation of the results from the EVOPACS study is limited by the small sample size and short (8-week) follow-up. The clinical experts consulted by CADTH did not consider the exclusion of patients with their most recent MI or stroke being within 4 weeks of randomization to be a major gap in the evidence. The clinical experts advised that patients with an index case of ACS are not likely to be initiated on evolocumab in the in-patient setting as they are most likely to be statin-naïve, which was the case for this study as well, where 80% and 76% patients in the evolocumab and placebo arms were statin-naïve, respectively. As a result, these patients will first be stabilized on a statin before considering any add-on therapies. Nonetheless, the clinical experts expect that patients with acute MI and who are stabilized will likely respond to treatment with evolocumab in a similar manner to patients with non-acute MI.

While most of the baseline characteristics were similar between the treatment groups, there was a slight imbalance in the index ACS events (i.e., for NSTE-ACS, there were 57% and 70% patients in the evolocumab group and placebo group, respectively, for STEMI, there were 43% and 30% patients in the evolocumab group and placebo group, respectively). Further, in consideration of an active smoking status being a major risk factor for CV events in the FOURIER trial, it should be noted that the active smokers were higher in the evolocumab group (41%) compared to the placebo group (30%).

Economic Evidence

Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model
Target population	Adults with recent acute coronary syndrome (ACS) within the past 1 year who have LDL-C ≥ 1.8 mmol/L despite taking moderate-to-high intensity statin therapy, with or without ezetimibe.
Treatment	Evolocumab as an adjunct to optimized background lipid-lowering therapy (LLT)
Dose regimen	Evolocumab administered as 140 mg every 2 weeks or 420 mg once monthly.
Submitted price	Evolocumab: $271.27 per 140 mg/mL single-use prefilled autoinjector Evolocumab: $587.75 per 120 mg/mL single-use automated mini-doser
Submitted treatment cost	Annual per-patient cost: $7,053
Comparator	Optimized background LLT, comprising moderate-to-high intensity statin therapy with or without ezetimibe.
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (52 years)
Key data sources	• Real world evidence database analysis from Alberta to inform baseline characteristics and CV event rates. • FOURIER trial to inform LDL-C reduction • Subgroup analyses from the FOURIER trial to inform relationship between treatment with evolocumab and CV event risk • Published literature to support the association between LDL-C and CV event risk, and subsequent CV event risk
Key limitations	• The relationship between treatment with evolocumab and CV events is uncertain due to limitations in the subgroup analyses conducted using data from the FOURIER and FOURIER-OLE trials including that multiplicity was not accounted for and in the subgroup analyses and that the sample size calculation was not done for the subgroup analyses. As a result, the incremental health benefits and costs associated with evolocumab are uncertain. • There are barriers to treatment adherence for LLTs including patient, healthcare system, and treatment-related factors. While research on LLT adherence has largely been focused

Component	Description
	on statin therapies, it remains unknown what the long-term adherence to newer treatments like evolocumab would be. Treatment discontinuation after three years was not assessed in the submitted model and thus the impact of treatment discontinuation on the cost-effectiveness of evolocumab is unknown. • The sponsor assumed that patients received the full benefit of LDL-C reduction observed at 48 weeks in the FOURIER trial for up to 52 years if they remained on treatment, and did not explore the impact of potential treatment waning over time. While clinical experts consulted by CADTH agreed that this may be a reasonable assumption, CADTH notes that 90% of the sponsor's predicted incremental health benefit are accrued beyond the time period for which there are data. • The sponsor considered patients with recent ACS (myocardial infarction [MI] or unstable angina) in the model. However, the evidence used to inform clinical efficacy in the model was predominantly from patients with history of MI only. As such, the cost-effectiveness of evolocumab in patients with unstable angina is uncertain. • The submitted model lacked transparency, relying on data held across multiple worksheets that were poorly organized. As a result, thorough auditing of the sponsor's model was not possible.
CADTH reanalysis results	• Key limitations of the sponsor's model could not be adequately addressed due to the lack of alternative data and limitations with the model structure (i.e., treatment waning and treatment discontinuation). As such, the sponsor's base case was maintained. • Sponsor's results: ICER = $87,882 per QALY gained (incremental costs: $78,856; incremental QALYs: 0.90) • Based on the sponsor's analysis, evolocumab is not cost-effective at a $50,000 per QALY gained threshold. A price reduction of 50% would be required to ensure cost-effectiveness.
Key scenario analyses	• CADTH conducted two scenario analyses using different values for CV-related mortality: 1) the lower credible interval of the hazard ratio for CV mortality from the FOURIER-OLE trial (i.e., the greatest mortality benefit), and 2) the upper credible interval (i.e., the smallest mortality benefit). • In CADTH scenario analysis 1 (assuming the greatest mortality benefit), evolocumab was associated with an ICER of $68,809 per QALY gained compared to optimized background LLT alone. In CADTH scenario analysis 2 (assuming the smallest mortality benefit), evolocumab was associated with an ICER of $164,205 per QALY gained.

ICER = incremental cost-effectiveness ratio; LLT = lipid-lowering therapy; LY = life-year; QALY= quality-adjusted life-year.

Budget Impact

CADTH identified the following key limitations with the sponsor's analysis: the sponsor's estimation of the eligible population using a prevalence-based approach was inappropriate; the market uptake of evolocumab is uncertain. The CADTH reanalysis included applying an incidence-based approach using the annual incidence of MI, adjusted for the incidence of UA to estimate the eligible population. Based on the CADTH reanalysis, the three-year budget impact to the public drug plans of reimbursing evolocumab as an adjunct to optimized LLT for the proposed indication is expected to be $127,964,628 (Year 1: $31,417,178; Year 2: $42,551,826; Year 3: $53,995,624).

CDEC Information

Members of the Committee:

Dr. James Silvius (Chair), Dr. Sally Bean, Mr. Dan Dunsky, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Trudy Huyghebaert, Dr. Peter Jamieson, Mr. Morris Joseph, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Dr. Danyaal Raza, Dr. Edward Xie, and Dr. Peter Zed.

Meeting date: April 24, 2024

Regrets:

2 expert committee members did not attend.

Conflicts of interest:

None