CADTH REIMBURSEMENT REVIEW

Patient and Clinician Group Input

evolocumab (Repatha)

(Amgen Canada Inc.)

Indication: Repatha is indicated for the reduction of elevated LDL-C in adult patients with primary hyperlipidemia (including heterozygous familial hypercholesterolemia 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 as an adjunct to diet, alone or in combination with non-statin lipid-lowering therapies, in patients for whom a statin is contraindicated

October 3, 2023

This document compiles the input submitted by patient groups and clinician groups for the file under review. The information is used by CADTH in all phases of the review, including the appraisal of evidence and interpretation of the results. The input submitted for each review is also included in the briefing materials that are sent to expert committee members prior to committee meetings.

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Clinician Input

Clinician Group: Concerned Physicians across Canada

CADTH Project Number: SR0821-000

Generic Drug Name (Brand Name): Evolocumab (Reptha)

Indication: Primary Hyperlipidemia and Prevention of cardiovascular events

Name of Clinician Group: Concerned Physicians across Canada

Author of Submission: Dr. Jeffrey Habert MD CCFP FCFP, Assistant Professor, University of Toronto, DFCM

1. About Your Clinician Group

We are a group of primary care and specialist physicians that treat CAD/ACS, educate physicians about same, and want the best treatment available for our patients to reduce cardiovascular risk in the critical post ACS period.

2. Information Gathering

Current nationally recognized Evidence based guidelines (CCS) demonstrate evidence of imminent risk in the post ACS period that can be reduced with evolocumab. In addition, we used evidence from RCTs that are published in high impact peer-reviewed journals.

3. Current Treatments and Treatment Goals

Current Canadian (2021) Lipid Guidelines delineate the treatment algorithm for high risk patients, and clearly suggest the use of PCSK9i in patients that have not reached a threshold level of LDL (below 1.8 mmol/L) on maximally tolerated statin +/- ezetimibe.

These recommendations are based on the ODYSSEY OUTCOMES and FOURIER trials with alirocumab and evolocumab (respectively).

Alirocumab (ODYSSEY OUTCOMES): Inclusion: ACS in last 12 months and maximally tolerated dose of statin: demonstrated statistically significant reduction in MACE-4 (0.85, CI0.78-0.93)) and MACE-3 (0.86, CI 0.79-0.93). There was also a nominal significant reduction in CV death (0.85, CI 0.73-0.98, p value 0.026)

Evolocumab (FOURIER): Clinically evident ASCVD (MI, Stroke, PAD: demonstrated statistically significant reduction in MACE-5 (0.85, CI 0.79-0.92) and MACE-3 (0.80, CI 0.73-0.88).

Subanalysis of FOURIER data (Gencer et. al. JAMA Cardiol, published online May 20, 2020) that looked at immediate post MI (1 to 12 months) patients versus remote MI (greater than 12 months) yielded a more robust risk reduction for primary outcome (0.81, CI 0.70-0.93, p=0.004) with ARR 3.7%, NNT 27 over 3 years in the immediate post MI group versus remote MI patients (0.92, CI 0.84-1.01, p=0.08, with ARR 1.1%). This demonstrates the need for rapid and “lowest is best” LDL lowering in the highest risk patients that are immediately post MI.

Best evidence for post ACS treatment in Canada is outlined by the Canadian Cardiovascular Society guidelines. Relevant to lipid management, the most current document may be found at: https://doi.org/10.1016/j.cjca.2021.03.016. The recommended treatment algorithm specifies that following behavioral / lifestyle / dietary changes, regardless of lipid levels, high intensity statin should be initiated. If the threshold of LDL-C of < 1.8 mmol/L or apoB < 0.7 g/L or non HDL-C < 2.4 mmol/L is not reached on highest tolerated statin dose, treatment should be intensified with non-statin drugs starting with ezetimibe if near threshold or with a PCSK9i if greater than 15% above threshold. If threshold is not reached with either drug alone, then the highest tolerated statin dose should be combined

with both drugs. This a Strong Recommendation with High Quality evidence to reduce the incidence of subsequent major adverse cardiovascular events

Furthermore, FOURIER-OLE (open label extension) study (O'Donoghue, M et al. Circulation 2022;146:1109- 1119) was done to show data relating to increased time of treatment with evolocumab in patients with ASCVD. Specifically, 6635 patients who had completed the FOURIER trial with 2.2 years of treatment were eligible to continue with evolocumab (3355 patients who were originally taking evolocumab continued treatment, whereas 3280 patients who were taking placebo were started on evolocumab). The study continued for a median of 5 years. This increased the maximum exposure to evolocumab in both FOURIER and FOURIER-OLE to 8.4 years. At 12 weeks into the study, the median LDL was 0.77 mmol/L. The study showed that patients that had started evolocumab earlier (as in the parent FOURIER trial) and maintained the therapy (through the FOURIER open label extension study) had a 15% reduction in MACE-5 (0.85, CI 0.75-0.96, p=0.008), 20% reduction in MACE-3 (0.80, CI 0.68-0.93, p=0.003), as well as a 23% statistically significant reduction in cardiovascular death (0.77, CI 0.60-0.99, p=0.04) when compared to patients that were in the placebo group in the FOURIER trial and transitioned to evolocumab in the OLE study. Moreover, there was no significant difference in serious adverse events, muscle related events, new-onset diabetes, hemorrhagic stroke, or neurocognitive events.

Taken in total, the body of evidence with PCSK9i use in ASCVD patients suggests the following:

1. Risk reduction for MACE 5 and MACE 3 in ASCVD patients including post ACS and stable CAD patients.
2. Increased benefit with higher relative and absolute risk reduction in highest risk patients such as immediately post MI (less than 12 months).
3. Extension study with evolocumab suggests the importance of earlier initiation of PCSK9i in the ASCVD journey results in lower cardiovascular outcomes, including CV death. This confirms the concept of both "the lower the better, and the earlier the better".
4. Extension study with maximum exposure to evolocumab of 8.4 years showed good safety and tolerability of long term PCSK9i use, as well as LDL lowering to less than 1 mmol/L, with no important safety signals seen

For maximum impact/benefit of PCSK9i in the Canadian ASCVD population for prevention of recurrent events, revascularization and CV death, we should offer treatment to the highest risk patients such as those immediately post ACS/MI.

4. Treatment Gaps (unmet needs)

Considering the treatment goals in Section 3, please describe goals (needs) that are not being met by currently available treatments.

High intensity statin therapy frequently does not achieve the lipid threshold specified above. For example, in the PROVE-IT TIMI 22 trial of post ACS patients, 37% failed to achieve LDL-C level of 1.8 mmol/L on atorvastatin 80 mg daily J Am Coll Cardiol. 2005 Oct, 46 (8) 1411–1416.

- Statins are not always initiated in the post ACS period and even when they are, the lipids are not being rechecked quick enough (ie within 3 months) to ascertain if the treatment threshold of LDL
- <1.80 has been reached.
- Ezetimibe not being added soon enough and, in many cases, NOT achieve threshold. If LDL >2.2, then consideration should be made to start evolocumab immediately and before ezetimibe as recommended by current CCS lipid guidelines.
- Not all patients respond adequately to or tolerate available treatments.
- Patients require other options if statin intolerant and cannot reach threshold on the highest tolerated statin dose.
- Some patients will be more adherent if medications are started in hospital which optimize adherence eg. daily pill versus monthly injectable
- Patients become refractory to current treatment options.
- No treatments are available to reverse the course of disease.

- No treatments are available to address key outcomes.
- Treatments are needed that are better tolerated.
- Treatments are needed to improve compliance.
- Formulations are needed to improve convenience.

Unmet need: Data

Real world data suggests that in Canada, threshold levels are not being reached in post AMI patients.

A study from Alberta (Scory, T et al. presented at Scientific Sessions, American College of Cardiology 2020) showed that amongst 26,040 of acute MI (AMI) patients in Alberta between April 2011 and March 2015, 6 months post MI, 63.5% of patients did not reach 2016 CCS dyslipidemia LDL-C targets (<= 2.0 mmol/L) pre MI and 29.8% did not reach it post AMI. This is an underestimate considering the 2021 CCS LDL-C threshold of 1.8 mmol/L. Only 58.8% of patients were on high intensity statins and 22.6% were not on any treatment, suggesting the possibility of statin intolerance.

PCSK9i real world Canadian data with evolocumab shows very good efficacy at lowering LDL-C added to statins, as well as very good persistence to evolocumab with no adverse events.

Zerbini registry (Gupta, M et al. CJC Open 4(2022) 558-567) showed 12 month data of evolocumab use in 131 Canadian patients both with ASCVD, FH or both (58% statin use). The study demonstrated an LDL-C reduction of 59%, with 78% of patients achieving LDL-C <1.8 mmol/L and 92% persistence with 0 adverse events reported

EVOPACS (Koskinas, K et al J Am Col Cardiol 2019 74(20):2452-2462) is a study of in hospital initiation of evolocumab added to moderate to high intensity statin 72 hours after AMI, with an 8 week follow-up in 308 patients. In hospital initiation of evolocumab post AMI was found to be well tolerated with no new safety findings. After 8 weeks 95.7% of patients on evolocumab and statin reached below LDL-C threshold of <1.8 mmol/L versus only 37.6% in the statin treated group.

In hospital treatment of post AMI patients with evolocumab add to of maximally tolerated statins would allow for more patients to lower LDL-C to appropriate levels, resulting in less recurrent events, re-hospitalization, and repeat procedures in our highest risk ASCVD patients. It would remove many barriers for LDL-C reduction (including statin intolerance, inertia in initiation and optimization that occurs in our current healthcare system). Many patients post AMI fall through the cracks in terms of post op follow-up and optimization of lipid lowering therapy.

5. Place in Therapy

5.1. How would the drug under review fit into the current treatment paradigm?

- As per requested reimbursement criteria: For patients with recent acute coronary syndrome (ACS), who have LDL-C ≥ 1.8 mmol/L despite optimized lipid-lowering therapy (moderate-to-high intensity statin therapy, with or without ezetimibe).
- Patients in the post ACS period need to have lipids optimized as soon as possible to decrease residual risk for future events (in addition to moderate-high intensity statin)
- The most ideal time to start would be in hospital to ensure immediate adherence.
- Evolocumab would NOT be first line, instead reserved for those the post ACS period not able to achieve lipid threshold as described.
- This is standard of care so does not change the current guideline-based treatment paradigm, that is currently limited by lack of coverage for ODB patients in the post ACS period.

The role of PCSK9i therapy in post ACS patients is clearly outlined in the 2021 Canadian Cardiovascular Society dyslipidemia guidelines as specified in Question 3

It is clearly established by 2021 CCS dyslipidemia guidelines that in ASCVD patients, add on therapy is required if LDL-C >1.8 mmol/L, or apoB>0.7 g/L or non-HDL>2.4 mmol/L with maximally tolerated ezetimibe, with a PCSK9i. We know that the lower the LDL-C, the less the likelihood of a recurrent event, and that extremely low LDL-C levels, even less than 1 mmol/L are safe. In general, plaque stabilization occurs at LDL-C of less than 1.8 mmol/L, and plaque regression can occur with LDL-C less than 1.29 mmol/L. PCSK9i, specifically evolocumab, has unequivocal data on reduction of CV death, MI, ischemic stroke, unstable angina and coronary revascularization. The effect is magnified in the very high risk population of immediate post AMI patients (within 12 months). Given the unmet gap of achieving LDL-C threshold, getting patients to stay on statins due to statin intolerance post MI, as well as the availability of effective PCSK9i therapy to bridge this gap, there should no longer be any excuse to leave very high risk patients untreated and at high risk of recurrent events and CV death. PCSK9i should be positioned as add on therapy in patients who cannot reach LDL-C threshold levels despite maximally tolerated statin and ezetimibe therapy in ASCVD patients, particularly those that are at the highest risk, including acute post MI patients. Ideally, to ensure that patients receive therapy, this should be done as close to the AMI event as possible, within the first month, or even in-hospital initiation.

5.2. Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

Indication as discussed: For patients with recent acute coronary syndrome (ACS), who have LDL-C ≥ 1.8 mmol/L despite optimized lipid-lowering therapy (moderate-to-high intensity statin therapy, with or without ezetimibe).

These can be easily identified with most recent LDL result and drug history (i.e. mod-high intensity statin +/- ezetimibe (according to guidelines, Apo-B >0.7 or non-HDL <2.4 would also indicate need)

Most patients for which the therapy is indicated will respond with an additional 50-60% LDL reduction on top of maximally treated statin therapy with or without ezetimibe.

No other tests are needed apart from LDL-C and in patients with TG levels greater than 1.5 mmol/L, consider using apoB, or non-HDL.

Calculated LDL-C levels via the Friedewald equation may underestimate LDL-C particularly in patients with high TG levels. In these cases, apoB or non-HDL cholesterol may represent a more accurate parameter to assess risk.

Lack of suitability: Although there is evidence that the lower the LDL-C the better at lowering risk of recurrent events, the indication that is being requested would target the highest risk patients (ie. started within 12 months post ACS, but maintained after this period if PCSK9i therapy is found to be effective) that do not achieve a LDL-C threshold of <=1.8 mmol/L or apoB>0.7 g/L or non-HDL>2.4 mmol/L despite maximally tolerated statin therapy with or without ezetimibe

5.3 What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

Measurement of a standard lipid profile including LDL-C, apo B and non-HDL cholesterol will definitely define treatment response if threshold levels are reached (ie LDL<1.80 or apoB>0.7 g/L or non-HDL>2.4 mmol/L. Follow up should be done 1 month after starting therapy and repeated if nonadherence is suspected.

5.4 What factors should be considered when deciding to discontinue treatment with the drug under review?

Discontinuation of therapy would simply lead to a rise in lipids to pre-treatment levels, resulting in an elevated residual risk that was similar to before starting the medication.

Adverse events felt to be secondary to evolocumab, although there are very few adverse effects of evolocumab, other than idiosyncratic allergic or local injection site reactions that would necessitate drug discontinuation.

5.5 What settings are appropriate for treatment with [drug under review]? Is a specialist required to diagnose, treat, and monitor patients who might receive [drug under review]?

Evolocumab should be started in hospital or community settings and NOT necessarily limited to specialists. If started in hospital immediately post ACS, likely a cardiologist or internist will initiate. However, many/most will be monitored by family physicians that are seeing their patient in the post-ACS period.

6. Additional Information

7. Conflict of Interest Declarations

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict of interest declaration is required for participation.

Declarations made do not negate or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

1. Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

No assistance from any commercial or no-commercial organization was received in the creation of this document.

2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

No assistance from any commercial or no-commercial organization was received in the collection or analysis of data used to create this document.

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. **Please note that this is required for each clinician who contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

Declaration for Clinician 1

Name: Jeffrey Habert

Position: Family Physician, Assistant Professor, University of Toronto, DFCM

Date: 28-10-2023

X☐ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 1: Conflict of Interest Declaration for Clinician 1

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**

Amgen		x		
Bayer		x		
Boehringer-Lilly			x	
Novartis	x			
HLS		x		
Novo-Nordisk		x		
Pfizer		x		
Thrombosis Canada	x			
Astra Zeneca	x			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 2

Name: Alan Bell MD FCFP

Position: Family Physician, Assistant Professor, University of Toronto, DFCM Date: 12-10-2023

X I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 2: Conflict of Interest Declaration for Clinician 2

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Amgen Canada			x	
Boehringer Ingleheim	x			
HLS therapeutics	x			
Novartis Canada		x		
Astra Zeneca		x		
Thrombosis Canada	x			
Canadian Cardiovascular Society	x			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 3

Name: Grace Chua MD, FRCPC, FACC

Position: Community Cardiologist, staff cardiologist Mackenzie Health, Richmond Hill and Vaughan, Ontario Date: <04-11-2023>

X☐ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 3: Conflict of Interest Declaration for Clinician 3

Company	Check appropriate dollar range*			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
Amgen Canada			X	
Bayer			X	
Boehringer Ingleheim-Lilly			X	
Novartis Canada			X	
HLS therapeutics		X		
Pfizer			X	
AstraZeneca		X		
NovoNordisk		X		
GSK		X		
Servier	X			
Bristol Myers Squibb Canada	X			
CHEP Plus	X			
Canadian Cardiovascular Society	X			
Canadian Heart Failure Society	X			

University of Toronto Heart and Stroke Richard Lewar Center of Excellence		X		
Canadian Medical and Surgical Knowledge Translation Research Group		X		
Canadian Collaborative Research Network	X			
EOCI		X		
Liv Agency		X		
CPD Network		X		
Sei Healthcare		X		

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 4

Name: Daniel Ngui, FCFP Position:
Family Physician Date:
18/10/2023

X I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 4: Conflict of Interest Declaration for Clinician 4

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Amgen	x			
Astra	x			
Valeo	x			
Novo		x		
Bayer			x	
Lilly	x			
BI		x		

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 5

Name: Marla Shapiro

Position: Family Physician, Professor, University of Toronto, DFCM Date: 18/10/2023

X I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 5

Company	Check appropriate dollar range*			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
Amgen	x			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 6

Name: Vivien Brown

Position: Family Physician, Assistant Professor, University of Toronto, DFCM Date: 18/10/2023

X I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 6: Conflict of Interest Declaration for Clinician 6

Company	Check appropriate dollar range*			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
Amgen	x			

* Place an X in the appropriate dollar range cells for each company.

Clinician Group: Western University, Division of Cardiology, Cardiac Rehabilitation and Secondary Prevention Program

CADTH Project Number: **SR0821-000**

Generic Drug Name (Brand Name): Evolocumab (REPATHA)

Indication: Present indication: REPATHA is indicated for the reduction of elevated LDL-C in adult patients with primary hyperlipidemia (including heterozygous familial hypercholesterolemia 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 as an adjunct to diet, alone or in combination with non-statin lipid-lowering therapies, in patients for whom a statin is contraindicated.

Indication for requested reimbursement criteria: Patients with recent acute coronary syndrome (ACS), who have LDL-C ≥ 1.8 mmol/L despite optimized lipid-lowering therapy (moderate-to-high intensity statin therapy, with or without ezetimibe).

Name of Clinician Group: Western University, Division of Cardiology, Cardiac Rehabilitation and Secondary Prevention Program

Author of Submission: Dr. Robert McKelvie, Dr. Neville Suskin & Dr. Ashlay Huitema

1. About Your Clinician Group

Comprehensive cardiac rehabilitation including secondary prevention care delivery.

2. Information Gathering

Literature review, group experience including program evaluation and publications.

3. Current Treatments and Treatment Goals

Annually, approximately 90,000 patients in Ontario and 250,000 patients in Canada are diagnosed with atherosclerotic cardiovascular disease (ASCVD), and as such are eligible for drug treatment for lipids to achieve LDL-C < 1.8 mmol/L as per the Canadian dyslipidemia guidelines (DOI: 10.1016/j.cjca.2018.07.413 & 10.1016/j.cjca.2021.03.016). In addition to prioritizing healthy lifestyle interventions, the use of pharmacotherapeutic options to treat eligible patients is recommended by the Canadian 2021 dyslipidemia guidelines to further reduce morbidity and mortality from ASCVD in Canada (DOI: 10.1016/j.cjca.2021.03.016).

4. Treatment Gaps (unmet needs)

4.1. Considering the treatment goals in Section 3, please describe goals (needs) that are not being met by currently available treatments.

In the real-world Canadian context lipid management is unsatisfactory. From 2010 to 2017, less than 30% of the 280,000 ASCVD patient cohort were taking the recommended dose intensity of statins and 34% were not taking statins at all (Chen et al, Can J Cardiol, 2019;35:884-891). Within 6-months following percutaneous coronary intervention between 2011 & 2014, only 52% of almost 48,000 patients in Ontario had their LDL-C measured, and 43% of those had LDL-C > 1.8 mmol/L. Compared to patients with LDL-C < 1.8 mmol/L, patients with LDL-C 1.8-2.6 & > 2.6, experienced MACE rates that were 20% & 80% higher respectively (Sud M et al. J Am Coll Cardiol. 2020; 76:1440-1450). A recent meta-analysis and meta-regression of randomized controlled trials of lipid-lowering

treatments achieving very low LDL-C levels demonstrated similar results (Patti et al, Euro Heart J – Cardiovasc Pharmacotherapy 2023; 9: 138-147). In this pooled analysis of 109,095 high risk patients with ASCVD those with LDL-C <1.0 mmol/l had a lower rate of major adverse cardiovascular events (OR 0.82, 0.72-0.94, P=0.005) versus those patients with higher LDL-C levels. Importantly the incidences of all safety outcomes were similar in the two groups for non-cardiovascular death (OR 1.13, 0.87-1.45, P=0.36), any adverse events (OR 1.00, 0.90-1.11, P=0.94) and adverse events leading to drug discontinuations (OR 1.00, 0.87-1.15, P=0.99). The results from these studies emphasize the importance of lowering LDL-C with effective therapy.

In our large (> 1,000 referrals annually) clinical cardiac rehabilitation practice, most patients are referred following a recent ASCVD event or procedure. At cardiac rehabilitation intake, which generally takes place within 2 months of the ASCVD event, 50% of patients have LDL-C values above 1.8 mmol/L. Six months later at cardiac rehabilitation program graduation, the proportion of patients remaining above the LDL-C target of 1.8 mmol/l is about 30%, and consequently these patients remain eligible for additional lipid lowering therapies according to the latest Canadian guidelines. This is despite our best efforts with lifestyle and behaviour change counseling along with aggressive implementation of available combination lipid lowering therapies. Consequently, treatments and treatment strategies are needed to reduce this care-gap.

5. Place in Therapy

5.1. How would the drug under review fit into the current treatment paradigm?

Presently evolocumab is indicated for the reduction of elevated LDL-C in adult patients with primary hyperlipidemia (including heterozygous familial hypercholesterolemia 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; also as an adjunct to diet, alone or in combination with non-statin lipid-lowering therapies, in patients for whom a statin is contraindicated. There are now robust data available supporting the use of evolocumab in patients with recent ACS, who have LDL-C ≥ 1.8 mmol/L despite optimized lipid-lowering therapy, with or without ezetimibe (Sabatine et al, N Engl J Med 2017; 376: 1713-1732). As stated evolocumab would not be used as first line therapy unless the patient could not tolerate statin therapy. The use of evolocumab is not expected to cause a shift in the current treatment paradigm. It would still be appropriate to recommend that patients try statin and ezetimibe therapy before initiating evolocumab therapy. The trials assessing the effectiveness and safety of evolocumab would support this approach.

It should be emphasized the mechanism of action for evolocumab is different than statin or ezetimibe and provides further reductions of LDL-C along with CV events. Mechanistic studies have demonstrated plaque stabilization and reduction. A study examined, using intravascular ultrasonography (IVUS) imaging, the effects of evolocumab on progression of coronary atherosclerosis in 968 statin treated patients (Nicholls et al JAMA 2016; 316: 2373-2384). The primary efficacy measure was the percent atheroma volume (PAV) and the secondary outcome efficacy measures were nominal change in normalized total atheroma volume (TAV) and percentage of patients demonstrating plaque regression. The evolocumab group, compared to place group, achieved a lower mean time-weighted LDL-C levels (0.95 mmol/l versus 2.4 mmol/l; difference 1.46 mmol/l. -1.55 mmol/l to -1.38 mmol/l, P<0.001). PAV increased 0.05% with placebo and decreased 0.95% with evolocumab (difference -1.0%, -1.8% to -0.64%, P<0.001). TAV decreased 0.9 mm^3 with placebo and 5.8 mm^3 with evolocumab (difference -4.9%, -7.3 mm^3 to -2.5 mm^3, P<0.001). Evolocumab induced plaque regression in a greater percentage of patients than placebo for PAV(64.3% versus 47.3%, difference 17%, 10.4% to 23.6%, P<0.001) and for TAV (61.5% versus 48.9%, difference 12.5%, 5.9% to 19.2%, P<0.001). Another study used optical coherence tomography (OCT) and IVUS to assess the effects of evolocumab on plaque composition following 52 weeks of treatment in 161 patients following MI (Nicholls et al, JACC Img 2022; 15: 1308-1321). The evolocumab group compared to the placebo group achieved lower LDL-C levels (0.73 mmo/l versus 2.26 mmol/l, P<0.001). There was a greater increase in the fibrous cap thickness with evolocumab compared to placebo (+42.7 µm versus +21.5 µm, P=0.015). The maximum lipid arc decreased more in the evolocumab group compared to the placebo group (-57.5º versus -31.4º, P=0.04). There was a greater regression of PAV observed with evolocumab versus placebo (-2.29% ± 0.47% versus -0.61% ± 0.46%, P=0.009). The findings from these studies provide mechanistic support for the beneficial effect on CV clinical outcomes observed with evolocumab. They also further emphasize the importance of initiating evolocumab early following a MI in patients that require greater LDL-C lowering to reduce the risk of subsequent CV events.

5.2. Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

Patients with demonstrated ASCVD, at high risk for recurrent cardiovascular events as demonstrated by recent ACS. These would be patients that have LDL-C levels ≥ 1.8 mmol/l despite adhering to appropriate healthy lifestyle choices as well as maximally tolerated statin and ezetimibe therapy.

5.3 What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

Typically, confirmation of treatment adherence and assessment of LDL-C levels are used to determine meaningful responses to therapy. Our experience with evolocumab for the cardiac rehabilitation patient population has been quite consistent with what has been observed in the clinical trials. There is a consistent significant lowering of LDL-C levels. The patients find the therapy convenient to use and our patients have not had any significant side effects. Therefore, in our real-world clinical experience with evolocumab we have found it to be efficacious, highly tolerable for the patients and is associated with a very acceptable safety profile.

5.4 What factors should be considered when deciding to discontinue treatment with the drug under review?

Adverse events

5.5 What settings are appropriate for treatment with [drug under review]? Is a specialist required to diagnose, treat, and monitor patients who might receive [drug under review]?

Any health care provider within the patient's circle of care could prescribe evolocumab for eligible patients.

6. Additional Information

The Further Cardiovascular Outcomes Research with PCSK9 inhibition in Subjects with Elevated Risk (FOURIER) trial examined the clinical efficacy and safety when evolocumab was added to high-intensity or moderate-intensity statin therapy in patients with clinically evident ASCVD (Sabatine et al, N Engl J Med 2017; 376: 1713-1732). There were 27,564 patients with ASCVD and LDL-C levels ≥ 1.8 mmol/l who were receiving statin therapy randomized to evolocumab or placebo. The primary composite outcome was CV death, MI, stroke, hospitalization for unstable angina or coronary revascularization. The secondary composite outcome was CV death, MI or stroke. The LDL-C levels with evolocumab compared to placebo were reduced by 59% from a median value of 2.4 mmol/l to 0.78 mmol/l (P<0.001). there was a significant reduction of the primary composite outcome (HR 0.85, 0.79-0.92, P<0.001). The secondary composite outcome was also significantly reduced (0.80, 0.73-0.88, P<0.001). There was no significant difference between groups regarding adverse events including new-onset diabetes mellitus and neurocognitive events. A limitation to this study was the shorter follow up period compared to other lipid-lowering trials.

The FOURIER trial demonstrated that patients with MI within the last two years, patients with multiple prior Mis and patients with residual multivessel CAD were at significantly higher risk of CV events and tended to have a greater risk reduction with evolocumab (Sabatine et al, Circulation 2018; 138: 756-766). Patients with a recent ACS (within 12 months) are considered a very high-risk group of patients requiring intensive lipid-lowering therapy (Grundy et al, Circulation 2019; 139: e1082-e1143; Pearson et al, Can J Cardiol 2021; 37: 1129-1150). As part of the FOURIER trial, there was a prespecified secondary analysis to assess (1) the risks of major adverse CV events as a function of time from the date of qualifying MI and (2) determine the effect of evolocumab on CV outcomes in patients with an MI within 12 months (Gencer et al, JAMA Cardiol doi:10.1001/jamacardio.2020.0882). There were 22,320 patients with a known date of MI included in the analysis. In the placebo arm the FOURIER trial primary end point was higher in the recent MI (within 12 months) compared to the more remote MI (adjusted HR 1.45, 1.29-1.64; P<0.001). In patients with a recent MI, evolocumab significantly reduced the risk of the primary end point by19% (HR 0.81, 0.70-0.93). In the patients with a remote MI, evolocumab reduced the risk of the primary endpoint by 8% (HR 0.92, 0.84-1.01). These findings support the claim that patients with a recent MI are at higher risk of CV events and experience greater absolute risk reduction with evolocumab. This emphasizes the need to treat high-risk ASCVD patients early, with intensive lipid-lowering therapy.

Although evolocumab was demonstrated to reduce CV risk in high risk ASCVD patients with no significant increase in adverse events, further long-term data were required for evolocumab. The FOURIER Open-Label Extension (FOURIER-OLE) study was designed to acquire longer-term data on safety, tolerability, lipid levels and risk of CV events with continued evolocumab exposure after completion of the parent FOURIER trials (O'Donoghue et al, Circulation 2022; 146: 1109-1119). There were 6635 patients enrolled in FOURIER-OLE, 3355 originally randomized to evolocumab and 3288 originally randomized to placebo. The median follow up was 5.0 years and maximum exposure to evolocumab was 8.4 years. For those originally randomized to evolocumab the median follow up was 7.1 years and maximum was 8.7years. the median LDL-C level 12 weeks after the start of FOURIER=OLE was 0.78 mmol/l (IQR 0.49-1.24 mmol/l) and was similar regardless of the original treatment assignment. For patients originally randomized to evolocumab the decrease in LDL-C was consistent over the median long-term follow up of 7.1 years. During long-term follow up, the patients originally randomized to evolocumab versus placebo had a 15% lower risk of CV death, MI, stroke, or hospitalization for unstable angina or coronary artery revascularization (HR 0.85, 0.75-0.96), P=0.008). Importantly there was a 23% lower risk of CV death (HR 0.77, 0.60-0.99, P=0.04). There was no observed trend toward an increase in the incidence of serious adverse events, muscle-related events, new-onset diabetes mellitus, hemorrhagic stroke, or neurocognitive events with long-term evolocumab and rates did not exceed those for patients in the placebo arm during the parent study. These findings extend the original observations from the parent FOURIER trial demonstrating the long-term safety and tolerability of evolocumab. FOURIER-OLE demonstrates the importance of early initiation of evolocumab in high risk ASCVD patients. Patients originally randomized to evolocumab had a lower CV event rate, including lower CV death, compared to patients originally randomized to placebo and then started on evolocumab in FOURIER-OLE.

Further analysis of the FOURIER-OLE database was performed to explore the relationship between achieved LDL-C levels and the occurrence of long-term adverse CV and safety outcomes down to LDL-C <0.5 mmol/l (Gaba et al, Circulation 2023; 147: 1192-1203). Analyzing LDL-C as a continuous variable there was a relationship between lower achieved LDL-C levels, down to levels <0.5 mmol/l, and a lower risk of CV events. The risk of a CV event was 18% lower per 1.0 mmol/l lower achieved LDL-C level (HR 0.82, 0.75-0.90). When the analysis was increased to patients from the entire FOURIER and FOURIER-OLE cohorts the results were consistent showing benefit with lower LDL-C even <0.5 mmol/l. There was no associated increase in adverse events at even the lowest LDL-C levels. These findings represent the longest follow-up of one of the largest RCTS of lipid-lowering and its open-label extension study. A recent study level meta-analysis of 109,095 patients examined the effect of lipid-lowering treatments achieving very low LDL-C levels (<1.0 mmol/l) to investigate a possible association with adverse events and the potential clinical benefit (Patti et al, Euro Heart J-CV Pharmacotherapy 2023; 9: 138-147). The rates of major adverse CV events were lower in the very low LDL-C group (OR 0.82, 0.72-0.94. P=0.005). The incidences of all safety outcomes were not increased in the very low LDL-C group compared to the group with higher LDL-C levels. These findings provide further support to the effectiveness and safety of achieving low LDL-C levels but the duration of follow up was not as long as was achieved in the FOURIER program.

The FOURIER program of research clearly demonstrates the benefit of evolocumab to reduce CV event rates in high risk ASCVD patients without causing an increase in safety related outcomes. Overall, the accumulated data from FOURIER and FOURIER-OLE would support Amgen's submission requesting the additional reimbursement criteria of "Patients with recent ACS, who have LDL-C ≥ 1.8 mmol/L despite optimized lipid-lowering therapy (moderate-to-high intensity statin therapy, with or without ezetimibe)".

7. Conflict of Interest Declarations

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

1. Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

   No

2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

   No

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. **Please note that this is required for <u>each clinician</u> who contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

Declaration for Clinician 1

Name: Robert McKelvie

Position: Professor of Medicine, Div. Cardiology, Western University, Ontario, Canada

Date: 25-11-2023

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 1: Conflict of Interest Declaration for Clinician 1

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Novartis		X		
Amgen		X		
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 2

Name: Neville Suskin

Position: Professor of Medicine, Div. Cardiology, Western University, Ontario, Canada

Date: 25-11-2023

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 2: Conflict of Interest Declaration for Clinician 2

Company	**Check appropriate dollar range***

	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
Novartis (consultancy)			X	
HLS (Ad. Board/grant)			X	
Boehringer Ingelheim (grant)			X	

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 3

Name: Ashlay Huitema

Position: Assistant Professor of Medicine, Div. Cardiology, Western University, Ontario, Canada

Date: 25-11-2023

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 3: Conflict of Interest Declaration for Clinician 3

Company	Check appropriate dollar range*			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
Amgen	X			
Bayer Canada	X			
Boehringer Ingelheim	X			
Novartis	X			

* Place an X in the appropriate dollar range cells for each company.

Clinician Group: Cambridge Cardiac Rehab Program

CADTH Project Number: SR0821-000

Generic Drug Name (Brand Name): evolocumab

Indication: evolocumab

is indicated in adults with primary hypercholesterolemia (heterozygous familial and non-familial), as an adjunct to diet: • in combination with a statin or statin with other lipid-lowering therapies in patients unable to reach low density lipoprotein cholesterol (LDL-C) goals with the tolerated dose of a statin or, • alone or in combination with other lipid-lowering therapies.

Name of Clinician Group: Cambridge Cardiac Rehab Program

Author of Submission: A. Shekhar Pandey

1. About Your Clinician Group

Please describe the purpose of your organization. Include a link to your website (if applicable).

Cambridge Cardiac Rehab Program is the regional cardiac rehabilitation and prevention program for Cambridge and North Dumfries and surrounding region of Cambridge, Ontario. This not for profit program represents the health care providers providing high risk primary and secondary cardiovascular prevention services for our region. Our group frequently communicates to share best practices, collaborates on research and educational projects and meets through various forums including advisory board, conferences, CME and other events.

2. Information Gathering

Review of relevant literature and publications, expert opinion gathering as well as background knowledge in the area

3. Current Treatments and Treatment Goals

Currently Health Canada-approved treatments for cholesterol reduction and ASCVD prevention include statins, ezetimibe and PCSK9 monoclonal antibodies, bile acid sequestrants, in addition to dietary therapy consisting of reducing saturated fat intake and dietary cholesterol. All of these therapies are used in clinical practice as per the 2021 Canadian Cardiovascular Society (CCS) dyslipidemia guidelines. Other medications such as fibrates are not indicated for LDL-C lowering and do not reduce CV risk.

Statins, ezetimibe and bile acid sequestrants are covered under Ontario provincial formulariy for patients with ASCVD.

PCSK9 inhibitors are currently only covered by Ontario provincial formulary for patients with confirmed or probable homozygous or heterozygous familial hyperlipidemia (FH) refractory to statins and ezetimibe therapy although data from phase 3 cardiovascular outcomes trials with patients ASCVD patients without FH show significant morbidity and mortality reductions in ASCVD patients with the use of PCSK9 inhibitors like evolocumab on top of treatment with statins and ezetimibe when LDL still remains elevated.

4. Treatment Gaps (unmet needs)

Despite the availability of Statins, ezetimibe and bile acid sequestrants, a significant percentage of patients at risk for recurrent cardiovascular events due to ASCVD fail to achieve the targets for LDL as out lined in the CCS 2020 guidelines. This is in part due to failure of the agents covered by Ontario provincial drug formulary to achieve the low LDLs required, side effect profile / tolerability and patient adherence.

4.1. Considering the treatment goals in Section 3, please describe goals (needs) that are not being met by currently available treatments.

1. Tolerability. Many patients perceive side-effects to statins and ezetimibe, leading to therapy discontinuation. Therapies with lower rates of perceived side-effects are needed.

2. Treatment to target. Despite existing therapies, many patients do not reach their guideline recommended lipid target. This issue is increasing in importance because the latest version of many guidelines (including the 2020 Canadian Cardiovascular Society lipid guidelines) recommend treating LDL-C to even lower levels in high risk patients. Add-on therapies are therefore needed to allow patients to reach their lipid targets.

5. Place in Therapy

5.1. How would the drug under review fit into the current treatment paradigm?

The drug under review works by inhibiting PCSK9 protein by binding the PCSK9 protein in circulation. PCSK9 protein results in the degradation of LDL receptors on hepatocytes. By reducing circulating PCSK9 protein, the drug under review subsequently increases the density of hepatic LDL receptors. It would be most likely used as add-on to maximally tolerated doses of statins (and/or ezetimibe) in patients who require additional lipid lowering to achieve CCS 2021 LDL guidelines.

5.2. Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

1. Patients with ASCVD with other markers of high risk, including: recent MI, CABG, multi-vessel

disease, polyvascular disease, diabetes, elevated Lp(a) whoses LDL still remain above guideline recommended targets for established ASCVD.

2. Patients with statin intolerance

Which patients are most in need of an intervention?

Based on available data the response to the drug is highly uniform, and as such it would be suited to all patients who require additional LDL lowering. But in particular, wherein either lifetime or short-term CV risk is high, patients especially suited are those requiring secondary ASCVD prevention, patients with FH and patients with high risk such as those with DM or high Framingham Risk Score. This includes:

4. Patients with ASCVD with other markers of high risk, including: recent MI, CABG, multi-vessel CAD, peripheral vascular disease patients, polyvascular disease, diabetes, and elevated Lp(a) whose LDL remain above targets determined by Canadian guidelines.
5. Patients with partial statin tolerance that are unable to tolerate maximum dose statins and do not achieve target LDLs at the lower doses of statins that they do tolerate.

Would this differ based on any disease characteristics (e.g., presence or absence of certain symptoms, stage of disease)?

Patients not at target for LDL per CCS guidelines 2021 will benefit if they are on maximally tolerated statins +/- Ezetrimibe.

How would patients best suited for treatment with drug under review be identified (e.g., clinician examination/judgement, laboratory tests (specify), diagnostic tools (specify))

Patients would be identified based on their diagnosis ASCVD and the results of lipid testing (LDLC, non-HDL-C, apoB). These tests are widely available and used in practice routinely.

Are there any issues related to diagnosis?

No.

Is a companion diagnostic test required?

LDL measurement when on therapy with maximally tolerated statins +/- Ezetrimibe

Is it likely that misdiagnosis occurs in clinical practice (e.g., underdiagnosis)?

A significant number of high risk patients are not adequately identified in clinical practice due in part to a sense of futility since there have not been effective alternate therapies that are covered by provincial formularies.

Is it possible to identify those patients who are most likely to exhibit a response to treatment with drug under review?

Not that we are aware of. Based on available data, the response to the drug appears fairly uniform, and therefore the issue of non-response is likely not particularly relevant. In theory patients with a PCSK9 gain-of-function mutation have been shown to have a greater than average response, but they represent a very small percentage of patients and genetic testing for this is not clinically warranted.

5.3 What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

Are outcomes used in clinical practice aligned with the outcomes typically used in clinical trials?

LDL-C, non-HDL-C, and ApoB measurements all align with typical clinical practice and are endorsed by national guideline recommendations.

What would be considered a clinically meaningful response to treatment? Consider the magnitude of the response to treatment. Is this likely to vary across physicians?

At least a 30% reduction in LDL-C or non-HDL-C would be considered meaningful.

Examples: improved survival; reduction in the frequency/severity of symptoms (provide specifics regarding changes in frequency, severity, etc.); attainment of major motor milestones; ability to perform activities of daily living; improvement of symptoms; and stabilization (no deterioration) of symptoms.

Reductions in levels of LDL cholesterol, non-HDL cholesterol, and apolipoprotein B levels have been shown to reduce the risk of major adverse cardiovascular events and cardiovascular mortality.

5.4 What factors should be considered when deciding to discontinue treatment with the drug under review?

Examples: disease progression (specify, e.g. loss of lower limb mobility); certain adverse events occur (specify type/frequency/severity); or additional treatment becomes necessary (specify).

At least a 30% reduction in LDL-C or non-HDL-C would be considered meaningful. If a smaller reduction is noted, this may be a reason to re-evaluate the appropriateness of continuing this therapy.

5.5 What settings are appropriate for treatment with [drug under review]? Is a specialist required to diagnose, treat, and monitor patients who might receive [drug under review]?

Examples: Community setting, hospital (outpatient clinic), specialty clinic

If a specialist is required, which specialties would be relevant?

Specialty clinic, community setting, hospital or community outpatient clinic. This should not require a specialist consultation as LDL is measured routinely in primary care facilities. This drug should be able to be appropriately used by both primary care and specialist physicians. Many ASCVD patients are followed by a specialist (internist, cardiologist, etc), and it is expected this would be the most likely scenario in which the drug would be initiated.

6. Additional Information

Is there any additional information you feel is pertinent to this review?

Additional therapies to effectively lower LDL cholesterol are required to improve patient outcomes including reductions in ASCVD events and mortality.

7. Conflict of Interest Declarations

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   None.

Declaration for Clinician 1

Name: Amritanshu Shekhar Pandey

Position: Clinical adjunct professor, McMaster University, staff cardiologist (Cambridge Cardiac Rehab, Cambridge Memorial Hospital, and St. Mary's General Hospital)

Date: <22.11.2023>

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 1: Conflict of Interest Declaration for Clinician 1

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Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Amgen	x			
HLS Pharmaceuticals	x			
Novartis	x			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 2

Name: Eileen Jang

Position: Nurse Practitioner (Cambridge Cardiac Rehab, Cambridge Cardiac Care Centre)

Date: <22.11.2023>

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Table 2: Conflict of Interest Declaration for Clinician 2

Company	**Check appropriate dollar range***

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Add company name				
Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 3

Name: <Dr. Andrea Rowe>

Position: Staff Physician, Cambridge Memorial Hospital and Cambridge Cardiac Care Centre

Date: <22.11.2023>

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Table 3: Conflict of Interest Declaration for Clinician 3

Company	Check appropriate dollar range*			
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Add company name				
Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 4

Name: <Laura Kuehl>

Position: <RN>

Date: Nurse (Cambridge Cardiac Rehab, Cambridge Cardiac Care Centre

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Table 4: Conflict of Interest Declaration for Clinician 4

Company	Check appropriate dollar range*			
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Add company name				
Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 5

Name: <Christopher Lo>

Position: < Nurse Practitioner (Cambridge Cardiac Rehab, Cambridge Cardiac Care Centre >

Date: <22.11.2023>

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Table 5: Conflict of Interest Declaration for Clinician 5

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Add company name				

Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 6

Name: <Claudia Surd>

Position: < Nurse (Cambridge Cardiac Rehab, Cambridge Cardiac Care Centre >

Date: <22.11.2023>

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Table 5: Conflict of Interest Declaration for Clinician 5

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Add company name				
Add company name				
Add or remove rows as required				

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Clinician Group: Division of Cardiology, University of Ottawa Heart Institute

CADTH Project Number: SR0821-000

Generic Drug Name (Brand Name): evolocumab (Repatha)

Indication: Primary hyperlipidemia

Specific Request: For patients with recent acute coronary syndrome (ACS), who have LDL-C ≥ 1.8 mmol/L despite optimized lipid-lowering therapy (moderate-to-high intensity statin therapy, with or without ezetimibe).

Name of Clinician Group: Division of Cardiology, University of Ottawa Heart Institute

Author of Submission: Ruth McPherson, MD, FRCPC

1. About Your Clinician Group

The University of Ottawa Heart Institute provides tertiary cardiac care for Eastern Ontario. We currently treat 1500 to 2000 new patients presenting with acute coronary syndromes (ACS) each year. Our mandate is not only to provide acute cardiac care but to ascertain that cardiac risk factors, including hypercholesterolemia, are appropriately treated to mitigate against further cardiac events.

2. Information Gathering

The information provided derives from a comprehensive literature search of peer-reviewed journals.

3. Current Treatments and Treatment Goals

Health behavior modifications remain the cornerstone of atherosclerotic cardiovascular disease (ASCVD) prevention. In addition to smoking cessation and physical exercise, these include a reduction in dietary saturated fat and cholesterol to lower LDL-cholesterol, a reduction in sugar and other refined carbohydrates to reduce abdominal obesity and its associated risk factors, including triglyceride-rich lipoproteins and diabetes.

In individuals with and without clinical ASCVD, studies consistently demonstrate a 20-22% ASCVD relative risk reduction (RRR) for each 1 mmol/L reduction in low-density lipoprotein cholesterol (LDL-C). This benefit is independent of the specific dietary or pharmacological intervention. The absolute benefit is a function of cardiovascular risk.

Statins are recommended as the initial pharmacological agent to reduce ASCVD events, based on efficacy, safety, and cost. Ezetimibe is a useful second agent for individuals not achieving adequate control on a maximally tolerated statin dose. Large randomized controlled trials (RCTs) demonstrate that statins significantly reduce ASCVD events and total mortality, proportional to the achieved LDL-C.

The approach is clearly stated in the 2021 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in Adults:

> *"We recommend use of high-intensity statin therapy in addition to appropriate health behaviour modifications for all secondary prevention CVD patients. For patients who do not tolerate a high-intensity statin, we recommend the maximally tolerated statin dose (Strong Recommendation; High-Quality Evidence)."*

A subset of high-risk individuals does not achieve adequate LDL-C control on statin/ezetimibe therapy and continue to experience myocardial infarction, stroke, heart failure and death.

PCSK9 targeted therapies are an appropriate *third line* approach for patients requiring additional LDL-lowering. The first PCSK9 inhibitors (evolocumab and alirocumab) are monoclonal antibodies that reduce LDL-C by 60% and in large RCTs, have been shown to reduce ASCVD events.

The FOURIER trial showed that the PCSK9 monoclonal antibody, evolocumab when added to statin therapy in patients with stable CAD, lowered LDL and significantly reduced the risk of cardiovascular events over a 3-year follow-up period and CV mortality over a subsequent 5 year period.

Gaba P, O'Donoghue ML, Park JG et al. Association Between Achieved Low-Density Lipoprotein Cholesterol Levels and Long-Term Cardiovascular and Safety Outcomes: An Analysis of FOURIER-OLE. Circulation. 2023;147:1192-1203.

Based on these data, the 2021 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in Adults stated

> *"We recommend intensification of lipid-lowering therapy with a PCSK9 inhibitor (evolocumab or alirocumab) – with or without the addition of ezetimibe – for secondary CV prevention patients shown to derive the largest benefit from PSCK9 inhibitor therapy in whom LDL-C remains ≥ 1.8 mmol/L (or non-HDL-C ≥ 2.4 mmol/L or ApoB ≥ 0.7 g/L) on maximally tolerated statin dose. (Strong Recommendation; Moderate-Quality Evidence)."*

Despite the incremental benefit of PCSK9 therapies, not all CVD patients are at equivalent risk. Given the desire for cost-effective medicine, subsequent analyses determined the subsets of patients with ASCVD enrolled in FOURIER who derived greater relative and/or absolute risk reduction from therapies. Over a 36-month follow-up period, patients with stable ASCVD with an LDL-C > 1.8 mmol/L on maximally tolerated statin therapy benefited from the addition of a PCSK9 therapy such as evolocumab.

However, the benefit was considerably greater, and the number needed to treat significantly lower in the high-risk population with a recent MI. Furthermore, the cumulative incidence curves appeared to diverge after only ≈6 months in the higher-risk subgroups versus after at least 12 months in the lower-risk subgroups (the clinician group refers to Figure 1 and Figure 2A in Sabatine et al. (2018), publicly accessible here).

Sabatine MS, De Ferrari GM, Giugliano RP et al. Clinical Benefit of Evolocumab by Severity and Extent of Coronary Artery Disease: Analysis From FOURIER. Circulation. 2018;138:756-766.

Gencer B, Mach F, Murphy SA et al. Efficacy of Evolocumab on Cardiovascular Outcomes in Patients With Recent Myocardial Infarction: A Prespecified Secondary Analysis From the FOURIER Trial. JAMA Cardiol. 2020;5:952-957.

Relevant to this request for restricted approval of evolocumab, the subset of ASCVD patients with a recent MI are at high absolute risk and show particular benefit when treated with a PCSK9 inhibitor in addition to statin therapy. By reducing recurrent events, health care savings can be anticipated in terms of hospital admissions, the need for percutaneous interventions or CABG, reduced risk of progressing to heart failure, death and disability.

4. Treatment Gaps (unmet needs)

4.1. Considering the treatment goals in Section 3, please describe goals (needs) that are not being met by currently available treatments.

The majority of ASCVD patients can achieve an LDL-C below 1.8 mmol/L with high dose statin therapy +/- ezetimibe.

However, a subset cannot achieve adequate lipid control due to:

- severe polygenic hypercholesterolemia
- inability to tolerate high dose statin therapy

- contraindication to high dose statin therapy, e.g. a history of statin induced hepatitis, underlying myopathy, severe chronic kidney disease

These patients, and particularly those at highest risk for recurrent CVD events, require additional LDL lowering treatment in the form of PCSK9 inhibitor therapy.

5. Place in Therapy

5.1. How would the drug under review fit into the current treatment paradigm?

Evolocumab is an appropriate third line approach for high risk patients who have had a recent ACS (within 12 mos) with an LDL-C level above 1.8 mmol/L despite maximally tolerated statin plus ezetimibe therapy.

Based on the findings of the FOURIER, GLAGOV and HUYGENS trials, addition of evolocumab can be expected to reduce MACE, elicit slow regression of underlying atherosclerosis and stabilize high risk plaques.

5.2. Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

Patients with clinical ASCVD most in need of addition of evolocumab to a maximally tolerated statin regimen are those with an LDL-C above 1.8 mmol/L and other high risk features, in particular a recent (within 12mos) myocardial infarction.

5.3 What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

Based on data from the FOURIER and FOURIER Long Term Open Extension study, a significantly lower recurrent event rate and need for hospitalization, percutaneous intervention or bypass surgery can be anticipated.

However, the measured outcome will be the percent decrease in LDL-C with the addition of evolocumab.

5.4 What factors should be considered when deciding to discontinue treatment with the drug under review?

Treatment with evolocumab would likely be discontinued at the discretion of the treating physician for reasons of futility such as diagnosis with another life limiting condition e.g. terminal cancer, severe dementia.

5.5 What settings are appropriate for treatment with [drug under review]? Is a specialist required to diagnose, treat, and monitor patients who might receive [drug under review]?

Treatment with evolocumab can be initiated by a cardiologist, lipid specialist or internist. Long term monitoring can be carried out by the primary care physician.

6. Additional Information

As a group, we wish to strongly emphasize that addition of evolocumab would clearly benefit a significant number of the 1500 to 2000 patients who present to the Ottawa Heart Institute each year with an acute coronary syndrome and continue to have levels of LDL cholesterol that put them at risk for recurrent events, despite treatment with maximally tolerated statin and other guideline directed therapies.

7. Conflict of Interest Declarations

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

4. Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

   No outside assistance.

5. Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

   No outside assistance.

6. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. **Please note that this is required for <u>each clinician</u> who contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

Declaration for Clinician 1

Name: Derek So, MD, FRCPC

Position: Professor of Medicine, Director Cardiac Catheterization Laboratory, University of Ottawa Heart Institute currently held

Date: 22-11-2023

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 1: Conflict of Interest Declaration for Clinician 1 (no COI)

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
No COI				

Declaration for Clinician 2

Name: Benjamin Chow, MD, FRCPC

Position: Professor of Medicine, Cardiologist, University of Ottawa Heart Institute

Date: 22-11-2023

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 2: Conflict of Interest Declaration for Clinician 2 no COI

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**

No COI				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 3

Name: Ruth McPherson, MD, PhD, FRCPC

Position: Professor of Medicine, Division of Cardiology, Director Lipid Clinic, Univ Ottawa Heart Institute

Date: 24-11-2-23

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 3: Conflict of Interest Declaration for Clinician 3

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Amgen (research grant)			X	
Amgen (advisory board)	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 4

Name: Aun Yeong Chong, MBBS, MD, FRCP(UK)

Position: Associate Professor of Medicine, Interventional Cardiologist, University of Ottawa Heart Institute

Date: 26-11-2023

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 4: Conflict of Interest Declaration for Clinician 4

Company	**Check appropriate dollar range***

	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
Abbott (Honorarium)		X		
Abbott (Advisory Board)	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 5

Name: Lloyd Duchesne, MD, FRCPC

Position: Associate Professor of Medicine, Cardiologist, University of Ottawa Heart Institute

Date: 26-11-223

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 1: Conflict of Interest Declaration for Clinician 5 No COI

Company	Check appropriate dollar range*			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
NONE				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 6

Name: Lyall Higginson, MD, FRCPC

Position: Professor of Medicine, Cardiologist, University of Ottawa Heart Institute

Date: 26-11-223

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 1: Conflict of Interest Declaration for Clinician 6 No COI

Company	Check appropriate dollar range*

	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
NONE				

* Place an X in the appropriate dollar range cells for each company.

Clinician Group: McMaster Lipid Clinic

CADTH Project Number: SR0821-000

Generic Drug Name (Brand Name): Evolocumab

Indication: Primary Hyperlipemia

Name of Clinician Group: McMaster Lipid Clinic

Author of Submission: Guillaume Pare

1. About Your Clinician Group

Please describe the purpose of your organization. Include a link to your website (if applicable).

We are an academic lipid clinic serving a population of 1M in the Hamilton, ON area. Our clinic serves as a referral center for both primary and secondary cardiovascular disease (CVD) prevention, as well as complex dyslipidemias.

2. Information Gathering

Please describe how you gathered the information included in the submission.

Review of relevant literature and publications as well as background knowledge in the area.

3. Current Treatments and Treatment Goals

Please describe the current treatment paradigm for the disease.

Focus on the Canadian context.

Please include drug and non-drug treatments.

Drugs without Health Canada approval for use in the management of the indication of interest may be relevant if they are routinely used in Canadian clinical practice. Treatments available through special access programs are relevant. Are such treatments supported by clinical practice guidelines?

Do current treatments modify the underlying disease mechanism? Target symptoms?

What are the most important goals that an ideal treatment would address?

Examples: *Prolong life, delay disease progression, improve lung function, prevent the need for organ transplant, prevent infection or transmission of disease, reduce loss of cognition, reduce the severity of symptoms, minimize adverse effects, improve health-related quality of life, increase the ability to maintain employment, maintain independence, reduce burden on caregivers.*

Treatment of primary hypercholesterolemia is currently based on statins (first line therapy), ezetimibe and PCSK9 monoclonal antibodies, in addition to dietary advice consisting of reducing saturated fat intake, increasing fiber intake and adapting a generally healthy and balanced diet. These recommendations are endorsed by the Canadian Cardiovascular Society dyslipidemia guidelines. Other medications include bile acid sequestrants and niacin but are seldom used due to poor tolerance and lack of evidence for CV risk reduction (niacin). Overarching treatment goal is to optimize CVD risk through reduction in LDLc / apoB / non-HDLc.

There is now irrefutable proof from randomized control trials (RCT), genetic studies and epidemiological studies that cholesterol and in particular LDLc have a causal role in atherosclerotic cardiovascular disease (ASCVD). Indeed, multiple RCTs, including the FOURRIER trial of evolocumab versus placebo, have demonstrated the safety and efficacy of LDLc lowering across a wide spectrum of baseline and achieved LDLc. This is reflected by current guidelines recommending LDLc < 1.8 mmol/L (Canada and USA) or even < 1.4 mmol/L (Europe) in post-ACS patients.

4. Treatment Gaps (unmet needs)

4.1. Considering the treatment goals in Section 3, please describe goals (needs) that are not being met by currently available treatments.

Please describe goals (needs) that are not being met by currently available treatments. Examples of unmet needs:

- *Not all patients respond to available treatments*
- *Patients become refractory to current treatment options*
- *No treatments are available to reverse the course of disease*
- *No treatments are available to address key outcomes*
- *Treatments are needed that are better tolerated*
- *Treatments are needed to improve compliance*
- *Formulations are needed to improve convenience*

Please describe limitations associated with current treatments (e.g., adverse events, administration, etc., if applicable).

Unfortunately, many patients are unable to meet treatment goals. The main reasons are:

- Intolerance to currently available treatments, particularly statins
- Variable response to currently available treatments (e.g. statins, ezetimibe)
- Lack of accessibility (i.e. cost) to highly effective PCSK9 inhibitors.

From the patient's perspective, the inability to access proven therapies following an event as traumatic as an acute coronary syndrome (ACS) can be extremely frustrating and distressing. It is our ethical duty to prioritize their well-being by making these therapies accessible and affordable, thereby enhancing their chances of a full and healthy recovery.

5. Place in Therapy

5.1. How would the drug under review fit into the current treatment paradigm?

Is there a mechanism of action that would complement other available treatments, and would it be added to other treatments?

Is the drug under review the first treatment approved that will address the underlying disease process rather than being a symptomatic management therapy?

Would the drug under review be used as a first-line treatment, in combination with other treatments, or as a later (or last) line of treatment?

Would the drug under review be reserved for patients who are intolerant to other treatments or in whom other treatments are contraindicated?

Is the drug under review expected to cause a shift in the current treatment paradigm?

Please indicate whether or not it would be appropriate to recommend that patients try other treatments before initiating treatment with drug under review. Please provide a rationale for your perspective.

Use of PCSK9 inhibitors such as evolocumab is already recommended by the CCS 2021 Lipids Guidelines as second or third line therapy (after statins and ezetimibe) in post-ACS patients with LDLc > 1.8 mmol/L. These guidelines are based on a careful review of current evidence and consistent with other guidelines worldwide. Unfortunately, we are unable to follow these guidelines in a significant proportion of patients because PCSK9 inhibitors are financially inaccessible without private insurance.

5.2. Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

Which patients are most likely to respond to treatment with drug under review?

Which patients are most in need of an intervention?

Would this differ based on any disease characteristics (e.g., presence or absence of certain symptoms, stage of disease)?

How would patients best suited for treatment with drug under review be identified (e.g., clinician examination/judgement, laboratory tests (specify), diagnostic tools (specify))

Are there any issues related to diagnosis?

Is a companion diagnostic test required?

Is it likely that misdiagnosis occurs in clinical practice (e.g., underdiagnosis)?

Is it possible to identify those patients who are most likely to exhibit a response to treatment with drug under review?

While all secondary prevention patients would benefit from LDLc control, patients at high absolute risk of event will undoubtedly benefit most in terms of absolute risk reduction. These patients have been labeled “high PCSK9 inhibitor benefit” in the 2021 CCS Lipids Guidelines and comprise patients with either a recent (<52 weeks) ACS or ASCVD with any of the following: Diabetes or metabolic syndrome / polyvascular disease / symptomatic peripheral arterial disease / recurrent MI / MI in the past 2 years / previous CABG surgery / LDL-C > 2.6 mmol/L or heterozygous familial hypercholesterolemia.

Of these “high PCSK9 inhibitor benefit”, the recent post-ACS group stands out as being at particularly high risk. Indeed, despite great advances in treatment and prevention of ASCVD, risk remains very high (17.2% vs 14.4% in patients with more distant events in FOURRIER). Fortunately, these patients also derived a greater benefit from early and aggressive lipid lowering (19% reduction versus 8%; NNT=27).

5.3 What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

Are outcomes used in clinical practice aligned with the outcomes typically used in clinical trials?

What would be considered a clinically meaningful response to treatment? Consider the magnitude of the response to treatment. Is this likely to vary across physicians?

Examples: improved survival; reduction in the frequency/severity of symptoms (provide specifics regarding changes in frequency, severity, etc.); attainment of major motor milestones; ability to perform activities of daily living; improvement of symptoms; and stabilization (no deterioration) of symptoms.

Treatment response is easy to assess with measurement of LDLc / apoB / non-HDLc pre- and post-treatment initiation. Response to treatment can be assessed ~ 4 weeks after treatment initiation and yearly thereafter.

5.4 What factors should be considered when deciding to discontinue treatment with the drug under review?

Examples: disease progression (specify, e.g. loss of lower limb mobility); certain adverse events occur (specify type/frequency/severity); or additional treatment becomes necessary (specify).

Lipid lowering therapy seldom needs to be discontinued. Factors to consider: (1) substantial changes in lifestyle and diet with reduction in need for lipid lowering therapy, and (2) clinically significant local reactions at the injection site.

5.5 What settings are appropriate for treatment with [drug under review]? Is a specialist required to diagnose, treat, and monitor patients who might receive [drug under review]?

Examples: Community setting, hospital (outpatient clinic), specialty clinic

If a specialist is required, which specialties would be relevant?

A specialist is not needed. Treatment could be prescribed by family physicians, cardiologists, endocrinologists, vascular medicine specialists and lipidologists. Evolocumab can be self-administered by patients after appropriate training.

6. Additional Information

Is there any additional information you feel is pertinent to this review?

N/A

7. Conflict of Interest Declarations

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

7. Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

   N/A

8. Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

   N/A

9. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. **Please note that this is required for each clinician who contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

Declaration for Clinician 1

Name: Guillaume Pare

Position: Professor, McMaster University

Date: 26-11-2023

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 1: Conflict of Interest Declaration for Clinician 1

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Amgen			X	
Novartis			X	

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 2

Name: Marie Pigeyre

Position: Assistant Professor, McMaster University

Date: 26-11-2023

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 2: Conflict of Interest Declaration for Clinician 2 – NO DISCLOSURE TO DECLARE

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Add company name				
Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 3

Name: <Enter full name>

Position: <Enter currently held position>

Date: <DD-MM-YYYY>

☐ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 3: Conflict of Interest Declaration for Clinician 3

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Add company name				
Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 4

Name: <Enter full name>

Position: <Enter currently held position>

Date: <DD-MM-YYYY>

☐ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 4: Conflict of Interest Declaration for Clinician 4

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Add company name				
Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 5

Name: <Enter full name>

Position: <Enter currently held position>

Date: <DD-MM-YYYY>

☐ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 5

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Add company name				
Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Clinician Group: British Columbia Lipid Specialists

CADTH Project Number: SR0821-000

Generic Drug Name (Brand Name): Evolocumab

Indication: Patients with recent acute coronary syndrome (ACS), who have LDL-C ≥ 1.8 mmol/L despite optimized lipid-lowering therapy (moderate-to-high intensity statin therapy, with or without ezetimibe)

Name of Clinician Group: British Columbia Lipid Specialists

Author of Submission: Liam Brunham

1. About Your Clinician Group

Please describe the purpose of your organization. Include a link to your website (if applicable).

This is group consists of the lipid specialists and physicians working in lipid clinics in British Columbia, including the Healthy Heart Program Prevention clinic at St. Paul's Hospital, the Surrey Lipid Clinic at Surrey Memorial Hospital, and the Vascular risk & Prevention clinic at Royal Jubilee Hospital. Our group shares best practices, collaborates on research and educational projects and meets through various forums including conferences, CME and other events.

2. Information Gathering

Please describe how you gathered the information included in the submission.

Review of relevant literature, conference presentations, and clinical experience with evolocumab since its release in Canada and background knowledge in the area.

3. Current Treatments and Treatment Goals

Please describe the current treatment paradigm for the disease.

Focus on the Canadian context.

Please include drug and non-drug treatments.

Drugs without Health Canada approval for use in the management of the indication of interest may be relevant if they are routinely used in Canadian clinical practice. Treatments available through special access programs are relevant. Are such treatments supported by clinical practice guidelines?

Do current treatments modify the underlying disease mechanism? Target symptoms?

What are the most important goals that an ideal treatment would address?

Examples: *Prolong life, delay disease progression, improve lung function, prevent the need for organ transplant, prevent infection or transmission of disease, reduce loss of cognition, reduce the severity of symptoms, minimize adverse effects, improve health-related quality of life, increase the ability to maintain employment, maintain independence, reduce burden on caregivers.*

Currently Health Canada-approved treatments include statins, ezetimibe and PCSK9 monoclonal antibodies, and inclisiran, in addition to dietary therapy consisting of reducing saturated fat intake and dietary cholesterol. All of these therapies are routinely used in clinical

practice and endorsed in the 2021 Canadian Cardiovascular Society dyslipidemia guidelines. Other medications such as fibrates are not indicated for LDL-C lowering and do not reduce CV risk. Bile acid resins are seldom used due to poor tolerance and poor LDL-C lowering properties and little evidence for CV risk reduction is available.

All of these therapies reduce levels of LDL-C and apoB. Certain of these therapies (namely statins, ezetimibe, and PCSK9 monoclonal antibodies) have been demonstrated to reduce cardiovascular events. Statins and evolocumab have both been demonstrated to reduce cardiovascular mortality.

4. Treatment Gaps (unmet needs)

4.1. Considering the treatment goals in Section 3, please describe goals (needs) that are not being met by currently available treatments.

Please describe goals (needs) that are not being met by currently available treatments. Examples of unmet needs:

- *Not all patients respond to available treatments*
- *Patients become refractory to current treatment options*
- *No treatments are available to reverse the course of disease*
- *No treatments are available to address key outcomes*
- *Treatments are needed that are better tolerated*
- *Treatments are needed to improve compliance*
- *Formulations are needed to improve convenience*

Please describe limitations associated with current treatments (e.g., adverse events, administration, etc., if applicable).

There is currently a major gap in control of LDL-C and apoB levels in patients with recent MI. Several large registries, including from Canada, have shown that <50% of these high-risk patients achieve guideline-recommended lipid thresholds, and many patients discontinue statin therapy due to adverse effects. There is clearly a need for treatments that are better tolerated, improve compliance, and allow these high-risk patients to achieve their treatment goals.

5. Place in Therapy

5.1. How would the drug under review fit into the current treatment paradigm?

Is there a mechanism of action that would complement other available treatments, and would it be added to other treatments?

Is the drug under review the first treatment approved that will address the underlying disease process rather than being a symptomatic management therapy?

Would the drug under review be used as a first-line treatment, in combination with other treatments, or as a later (or last) line of treatment?

Would the drug under review be reserved for patients who are intolerant to other treatments or in whom other treatments are contraindicated?

Is the drug under review expected to cause a shift in the current treatment paradigm?

Please indicate whether or not it would be appropriate to recommend that patients try other treatments before initiating treatment with drug under review. Please provide a rationale for your perspective.

Evolocumab is and would continue to be used as an add on to statin therapy in patients that cannot achieve treatment goals in response to maximally tolerated doses of statin, with or without ezetimibe. In some patients, the maximally tolerated dose of a statin is no statin, and evolocumab would play a particularly important role in those patients because of the lack of other potent therapies.

5.2. Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

Which patients are most likely to respond to treatment with drug under review?

Which patients are most in need of an intervention?

Would this differ based on any disease characteristics (e.g., presence or absence of certain symptoms, stage of disease)?

How would patients best suited for treatment with drug under review be identified (e.g., clinician examination/judgement, laboratory tests (specify), diagnostic tools (specify))

Are there any issues related to diagnosis?

Is a companion diagnostic test required?

Is it likely that misdiagnosis occurs in clinical practice (e.g., underdiagnosis)?

Is it possible to identify those patients who are most likely to exhibit a response to treatment with drug under review?

This review is specific to patients with a recent acute coronary syndrome, whose LDL-C or apoB levels remain above threshold despite maximally tolerated doses of statins. This is a well described group of very high-risk patients. Diagnosis of ACS is generally unambiguous and would be made during hospitalization for treatment of the event. No specific companion diagnostics are required. Response to evolocumab is generally quite uniform and there is no way a priori to predict the degree of LDL-C lowering a patient will achieve.

5.3 What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

Are outcomes used in clinical practice aligned with the outcomes typically used in clinical trials?

What would be considered a clinically meaningful response to treatment? Consider the magnitude of the response to treatment. Is this likely to vary across physicians?

Examples: improved survival; reduction in the frequency/severity of symptoms (provide specifics regarding changes in frequency, severity, etc.); attainment of major motor milestones; ability to perform activities of daily living; improvement of symptoms; and stabilization (no deterioration) of symptoms.

Response to treatment would be assessed based on the reduction in LDL-C, non-HDL-C or apoB. Clinical trials have demonstrated that this translates to reductions in cardiovascular morbidity and mortality. Average response is ~50-60% reduction in LDL-C, but there is some degree of inherent biological variability. Requiring a minimum percent LDL-C reduction is not supported by clinical evidence and would lead to excessive administrative burden without a benefit to patients.

5.4 What factors should be considered when deciding to discontinue treatment with the drug under review?

Examples: disease progression (specify, e.g. loss of lower limb mobility); certain adverse events occur (specify type/frequency/severity); or additional treatment becomes necessary (specify).

Treatment is expected to be long term given the chronic nature of atherosclerotic cardiovascular disease. Discontinuation would be considered if a patient developed an adverse response, failed to respond to therapy, or if prevention of cardiovascular disease was no longer consistent with the patient's goals of care.

5.5 What settings are appropriate for treatment with [drug under review]? Is a specialist required to diagnose, treat, and monitor patients who might receive [drug under review]?

Examples: Community setting, hospital (outpatient clinic), specialty clinic

If a specialist is required, which specialties would be relevant?

Treatment would be initiated in a community physician office, hospital in patient setting, out patient clinic, or specialty clinic. Most patients with a recent ACS would be connected to a specialist, but a specialist would not be required to initiate treatment.

6. Additional Information

Is there any additional information you feel is pertinent to this review?

Evolocumab was approved by Health Canada for patients with atherosclerotic cardiovascular disease in 2015. However, current public reimbursement is restricted to patients with Heterozygous Familial Hypercholesterolemia. Over the past 8 years, the clinical community has developed extensive experience with evolocumab, and it has become an extremely important medication for high risk patients who require further LDL-C lowering beyond maximally tolerated statins. At the same time, new clinical trial data, such as FOURIER-OLE, have highlighted the longer term safety and the efficacy of evolocumab in reducing cardiovascular morbidity and mortality. However, the lack of public reimbursement has led to a highly inequitable situation in which only patients with private insurance or the means to pay have access to this agent while many of the patients who could benefit from it the most do not. We view it as a high priority that the public healthcare system provide greater and more equitable access to this medication for patients with atherosclerotic cardiovascular disease, including those with a recent acute coronary syndrome.

7. Conflict of Interest Declarations

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1. Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

   No.

2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

   No.

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. **Please note that this is required for <u>each clinician</u> who contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

Declaration for Clinician 1

Name *Liam Brunham*
Position *Associate Professor, UBC; Medical Lead, Healthy Heart Program Prevention Clinic, St. Paul's Hospital*
Date *July 12, 2023*

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Amgen	☒	☐	☐	☐
Novartis	☒	☐	☐	☐
HLS	☒	☐	☐	☐
Ultragenyx	☒	☐	☐	☐

Declaration for Clinician 2

Name *G B John Mancini*
Position *UBC Professor, Director, CardioRisk Clinic (Vancouver Hospital), Staff Physician Healthy Heart Program Prevention Clinic (St. Paul's Hospital)*
Date *July 12, 2023*

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Amgen	☐	☒	☐	☐
Sanofi	☐	☒	☐	☐
Novartis	☒	☐	☐	☐
HLS Therapeutics	☐	☒	☐	☐

Esperion	☒	☐	☐	☐

Declaration for Clinician 3

Name *Carolyn Margaret Taylor*
Position *Associate Professor, UBC, Medical Director, Cardiac Rehabilitation Program, St Paul's Hospital*
Date *July 12, 2023*

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Amgen	☒	☐	☐	☐
Novartis	☒	☐	☐	☐
Sanofi	☒	☐	☐	☐
Astra Zeneca	x			

Declaration for Clinician 4

Name *Christopher Franco*
Position *UBC Clinical Asst Professor,*
Director Vascular Risk & Prevention clinic, RJH,
Medical Director Heart Health, Island Health
Date *July 12, 2023*

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Bayer	☒	☐	☐	☐
Amgen	☒	☐	☐	☐

Novartis	☒	☐	☐	☐

Declaration for Clinician 5

Name *Peter Tan*
Position *Clinical Assistant Professor (UBC). Cardiologist Surrey Memorial Hospital. Consultant Lipid Clinic, Jim Pattison Outpatient Care and Surgery Centre*
Date *July 12, 2023*

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Amgen	☒	☐	☐	☐
Sanofi	☒	☐	☐	☐

Declaration for Clinician 6

Name *Gordon Francis*
Position *Professor of Medicine, University of British Columbia; Physician, Healthy Heart Program Prevention Clinic, St. Paul's Hospital, Vancouver, BC*
Date *July 12, 2023*

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
N/A	☐	☐	☐	☐

Declaration for Clinician 7

Name *Apoorva Bollu*
Position *UBC Clinical Assistant Professor, Consulting physician, Surrey Lipid Clinic*
Date *July 12, 2023*

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
AMGEN	☒	☐	☐	☐
Sanofi	☒	☐	☐	☐

Declaration for Clinician 8

Name *Iulia Iatan*
Position *Consulting physician, Healthy Heart Program, St. Paul's Hospital*
Date *July 12, 2023*

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
N/A	☐	☐	☐	☐
Sanofi	☒	☐	☐	☐
Novartis	☒	☐	☐	☐

Clinician Group: Canadian Dyslipidemia Guideline Committee

CADTH Project Number: SR0821-000

Generic Drug Name (Brand Name): Evolocumab Indication: LDL-C reduction post-ACS

Name of Clinician Group: Canadian Dyslipidemia Guideline Committee Authors of Submission: George Thanassoulis and Milan Gupta

1. About Your Clinician Group

The Canadian Cardiovascular Society (CCS) has produced clinical practice guidelines for the treatment and management of dyslipidemia since 2009. These guidelines have been most recently updated, to reflect new clinical evidence including randomized trials of new therapies, in 2021 (Pearson G *et al*, *Can J Cardiol*. 2021 Aug;37(8):1129). The CCS dyslipidemia guidelines primary panel, who review the evidence and make recommendations, consists of an expert group of cardiologists, endocrinologists, internists, lipidologists, family physicians, nurses and pharmacists with extensive expertise in the diagnosis and management of lipid disorders in Canada. These guidelines have been historically well-received by Canadian physicians and represent the standard-of-care in the field of dyslipidemia for physicians in Canada.

2. Information Gathering

The input provided here is based on a systematic and thorough review of the literature that was part of the 2021 CCS dyslipidemia guidelines that included detailed review of randomized trial evidence for management of dyslipidemia in the post-acute coronary syndrome (ACS) setting (including primary publications and subanalyses). The process for identifying relevant data and its evaluation is outlined in the guideline document but follows the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) standards. As part of this submission, we also considered and reviewed new evidence published since the release of our guideline document in 2021.

3. Current Treatments and Treatment Goals

Current treatments: Acute coronary syndromes, including myocardial infarction, continue to be a leading cause of death, disability and health care costs in Canada. Post-ACS, patients continue to have a substantial risk of recurrent events that is driven, in large part, by suboptimal control of cardiovascular risk factors, including LDL-C (and other apoB containing atherogenic lipoproteins). Overwhelming evidence from several sources over the past few decades, including epidemiology, genetics and randomized trials, suggests that early and aggressive lowering of LDL-C (and other apoB lipoproteins) is the cornerstone of cardiovascular prevention and among the most effective approaches to reduce recurrent cardiovascular events (Boren *et al Eur Heart J*. 2020 Jun 21;41(24):2313).

To optimize post-ACS care, several approaches are currently recommended including lifestyle modifications and pharmacotherapy. All patients post-ACS are recommended aggressive health behavior modifications to optimize diet (e.g. reduce saturated fat and cholesterol in diet), physical activity (e.g. increase exercise and cardiac rehabilitation) and other lifestyle factors (e.g. reduce weight, central obesity and metabolic syndrome) (Pearson G *et al*, *Can J Cardiol*. 2021 Aug;37(8):1129).

In addition, to these lifestyle approaches, high-potency statins are recommended as first-line agents based on several large trials demonstrating a reduction in ASCVD events (including CV death and all-cause mortality). Furthermore, more recent evidence has suggested that additional add-on therapy to further lower LDL-C (and other apoB particles) with ezetimibe and/or PCSK9 inhibitors, leads to additional reductions in ASCVD outcomes (Cannon CP et al *N Engl J Med*. 2015 Jun 18;372(25):2387; GG Schwarz et al *N Engl J Med* 2018; 379:2097; Sabatine MS et al *N Engl J* Med 2017; 376:1713).

Treatment goals: The totality of the evidence in the post-ACS patient population demonstrates that for each additional 1 mmol/L reduction in LDL-C there is a consistent 20-22% reduction in ASCVD outcomes, across all lipid-lowering therapies (statins, ezetimibe or PCSK9 inhibitors) (Boren *et al Eur Heart J*. 2020 Jun 21;41(24):2313). This reduction in events appears to continue throughout the

range of LDL-C values with no apparent plateau in reducing CV events. More recent subanalysis of the FOURIER trial with evolocumab demonstrated that on-treatment LDL-C values < 1.4 mmol/L and as low as 0.5 mmol/L had the lowest risk of recurrent ASCVD events (Giugliano RP et al Lancet 2017 Oct 28;390(10106):1962). Therefore, a treatment strategy of maximally lowering LDL-C in high-risk patients is now considered optimal. This is supported by treatment guidelines in several countries recommending more intensive LDL-C lowering with treatment goals that are similar to Canada (i.e. LDL-C ≤ 1.8 mmol/L as in the US) (Grundy S et al *Circulation.* 2019;139:e1082) or even more aggressive (LDL-C ≤ 1.4 mmol/L in Europe) (Mach F et al *Eur Heart J*, 2020; 41:111).

Based on these robust data, and especially the RCT evidence with PCSK9 inhibitors, which included patients with a prior CV event with an LDL-C ≥ 1.8 mmol/L on maximally tolerated statin therapy (with or without ezetimibe) which demonstrated improved CV outcomes, the CCS committee lowered the threshold for intensifying therapy to 1.8 mmol/L with the goal of achieving very low LDL-C in select high-risk patients (such as those with an ACS < 1 year).

Specifically, the 2021 CCS dyslipidemia guidelines (Pearson G *et al*, *Can J Cardiol*. 2021 Aug;37(8):1129) made the following recommendations for the management of the post-ACS patient:

We recommend use of high-intensity statin therapy in addition to appropriate health behaviour modifications for all secondary prevention CVD patients. For patients who do not tolerate a high-intensity statin, we recommend the maximally tolerated statin dose (Strong Recommendation; High-Quality Evidence).

We recommend intensification of lipid-lowering therapy with a PCSK9 inhibitor (evolocumab or alirocumab) – with or without the addition of ezetimibe – for secondary CV prevention patients shown to derive the largest benefit from PSCK9 inhibitor therapy in whom LDL-C remains ≥ 1.8 mmol/L (or non-HDL-C ≥ 2.4 mmol/L or ApoB ≥ 0.7 g/L) on maximally tolerated statin dose. (Strong Recommendation; Moderate- Quality Evidence).

4. Treatment Gaps (unmet needs)

Considering the treatment goals in Section 3, please describe goals (needs) that are not being met by currently available treatments.

There remains a large treatment gap in Canada due to the limited access to PCSK9 inhibitors for the post- ACS patient. As outlined above, the current standard of care in post-ACS care in most economically advanced countries is further treatment intensification (after maximally tolerated statins and/or ezetimibe) with a PCSK9 inhibitor.

There remains substantial variation in interindividual response to statin therapy (with or without ezetimibe) as well as side-effects, that limit the maximal tolerated statin dose, that leaves ~10-20% of post-ACS patients with on-treatment levels of LDL-C that are unacceptably elevated (i.e. ≥ 1.8 mmol/L or non-HDL-C ≥ 2.4 mmol/L or ApoB ≥ 0.7 g/L). These patients are at increased risk for recurrent ASCVD events, including recurrent MI, stroke, peripheral vascular disease (including limb loss) and death, as well as increased health care-costs (from repeat hospitalizations, angioplasty, bypass surgery). Based on randomized trials, these ASCVD events and health care costs can be mitigated by further aggressive lowering of LDL-C with PCSK9 inhibitors. As it currently stands, limited access to PCSK9 inhibitors due to lack of public coverage leaves a small but important minority of patients without further pharmacologic therapy options to optimize their post- ACS care. We strongly believe that the lack of public access for PCSK9 inhibitors for post-ACS patients in Canada is currently unacceptable and does a great disservice to these vulnerable patients.

PCSK9 inhibitors have been available in Canada since 2015 and have demonstrated excellent tolerability, efficacy, ease of administration and long-term compliance. Evolocumab leads to ~60% reduction in LDL-C and has demonstrated sustained effects in LDL-C lowering up to 7 years in the long-term (open-label) extension of the FOURIER trial with evidence of continued reduction in ASCVD events, including CV mortality, and no evidence of increase in adverse events (including myopathy and/or cognitive dysfunction) (O'Donoghue ML et al *Circulation*. 2022;146:1109). Evidence from intravascular imaging studies in the post- ACS patient, also demonstrate that PCSK9 inhibitors by achieving ultra-low LDL-C levels, stabilize plaque (i.e. by increasing fibrous cap thickness) and regress atherosclerotic lesions (i.e. by reducing lipid arc) providing important mechanistic insights into their benefits (Nicholls SJ et al *J Am Coll Cardiol Img*. 2022

Jul, 15 (7) 1308–1321). In our clinical experience with these agents, our patients have found the bi-weekly or monthly dosing schedule highly convenient and, overall, they have been highly satisfied with these agents leading to sustained compliance with long-term therapy. We therefore feel that these agents are a highly valuable therapy for post-ACS patients and meet an important unmet medical need for select high-risk patients.

5. Place in Therapy

How would the drug under review fit into the current treatment paradigm?

As outlined in the 2021 CCS dyslipidemia guidelines and in-keeping with the clinical trial evidence, PCSK9 inhibitors would represent an add-on therapy after initiating maximally-tolerated statin therapy (with or without ezetimibe) when the LDL-C remains ≥ 1.8 mmol/L (or non-HDL-C ≥ 2.4 mmol/L or ApoB ≥ 0.7 g/L) in the post-ACS patient (within 12 months of ACS).

This approach is concordant with the evidence-base from 2 large randomized trials evaluating PCSK9 inhibitors, which randomized patients to PCSK9 inhibitor or placebo after optimizing lipid management with maximally tolerated statin therapy (with or without ezetimibe) when the LDL-C remained ≥ 1.8 mmol/L. These trials demonstrated a ~15-20% relative reduction in ASCVD events over a relatively short time frame (median follow-up of 2-3 years).

It should be noted that PCSK9 inhibitors would therefore represent a second line (after maximal tolerated dose of statins) or third line (after statins and ezetimibe) option for select patients who cannot reach adequate LDL-C control with available agents. This substantially reduces the eligible pool of patients requiring such agents and limits their use to those at highest risk with the greatest unmet need and the greatest potential to benefit.

Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

Although all patients with prior ASCVD events have demonstrated reduction in future CV events with achievement of very-low LDL-C levels in randomized trials of PCSK9 inhibitors, several key subanalyses of these trials have demonstrated patient groups with a greater absolute benefit from these agents.

Based on these data, as part of the 2021 CCS guidelines, we highlighted the following patient groups with LDL-C ≥ 1.8 mmol/L (or non-HDL-C ≥ 2.4 mmol/L or ApoB ≥ 0.7 g/L**)** as being "high PCSK9 inhibitor benefit" (the clinician group refers to Table 3 in the 2021 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in Adults, publicly accessible here).

Of these patient groups, patients with a recent ACS are a particularly high-risk group that is easily identifiable by practicing clinicians across the country and would benefit substantially from additional lipid-lowering with PCSK9 inhibitors (after maximal statins and/or ezetimibe).

Based on the FOURIER subanalysis (Gencer B et al *JAMA Cardiol.* 2020;5(8):952**)**, patients with a recent ACS in the last 1 year have a 45% greater risk of recurrent events than those with a more remote event (17.2% vs 14.4%). More importantly, in patients with a recent MI in the last 1 year, evolocumab reduced risk by 19% as compared to 8% in those with a remote MI (> 1 year) resulting in an absolute risk reduction of 3.7% (number needed to treat = 27 to prevent one recurrent ASCVD event) (Gencer B et al *JAMA Cardiol.* 2020;5(8):952**)**. These data highlight that these patients with recent ACS within the last year are at an unacceptably high risk for recurrent ASCVD events and that evolocumab can significantly and effectively reduce this residual risk. This represents an important group of patients in Canada that cannot be optimally treated due to limited public coverage of PCSK9 inhibitors.

What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

Evolocumab exerts its cardiovascular benefits by neutralizing circulating plasma PCSK9 leading to reductions in LDL-C (and other apoB lipoproteins). Therefore, treatment response can be easily assessed clinically by measurement of on-treatment LDL-C (or non-HDL-C or apoB) levels and assessing the % reduction as compared to pre-treatment LDL-C levels. Optimal response from PCSK9 inhibitors is between 50-60% reduction in LDL-C at 3-6 months after starting therapy. A clinically meaningful response is > 20% reduction in LDL-C. Treatment response (and compliance) should be measured yearly with repeat lipid profile and compared to pre-treatment levels.

What factors should be considered when deciding to discontinue treatment with the drug under review?

Given the exceptional tolerability of PCSK9 inhibitors such as evolocumab, there are few reasons to discontinue therapy. Intolerance or allergy to evolocumab or poor treatment response (i.e. < 20% reduction in LDL-C) should lead to discontinuation of the drug. In

addition, development of life-limiting disease with estimated survival < 2 years (e.g. malignancy) or other disorders severely affecting quality of life (eg.

Advanced dementia, severe frailty) may be reasons to discontinue all lipid-lowering treatments.

What settings are appropriate for treatment with [drug under review]? Is a specialist required to diagnose, treat, and monitor patients who might receive [drug under review]?

Evolocumab (and other PCSK9 inhibitors) are well-tolerated, easily self-administered by the patient and have a relatively innocuous safety profile. In addition, patients receiving these agents, are generally not required to have any specific follow-up outside their standard post-ACS care, except for yearly assessment of LDL-C levels to evaluate for treatment response. Therefore, these agents can be prescribed and managed by all physicians and health care providers who manage patients in the post-ACS setting (including cardiologists, cardiac surgeons, endocrinologists, lipid specialists, family physicians, nurse practitioners and pharmacists). In general, these agents are initiated in the out-patient setting after the patient has been stabilized and discharged from hospital and treatment response to first and second-line therapies (i.e. statins and ezetimibe can been assessed (i.e. 4-6 weeks post discharge).

6. Additional Information

It should be noted that the current request is focused on improving public coverage for evolocumab for the recent ACS patient (within 1 year of hospitalization) who remains suboptimally treated with LDL-C $\geq$ 1.8 mmol/L despite maximally tolerated statins and/or ezetimibe. Although the writing group wholly endorses this approach and is strongly supportive of this indication, based on the available evidence that LDL-C lowering reduces ASCVD events, we would prefer broader access to these agents in Canada for all patients with prior ASCVD events. Nonetheless, we acknowledge that obtaining access for the highest risk patients with the greatest benefit, such as patients with recent ACS (within 1 year), would be a first step in the right direction and would provide an important subgroup of our patients with public access to a much-needed therapy.

7. Conflict of Interest Declarations

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict of interest declaration is required for participation.

Declarations made do not negate or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

1. Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

   No

2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

   No

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. **Please note that this is required for each clinician who contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

Declaration for Clinician 1

Name: George Thanassoulis MD MSc FRCPC **Position:** Professor of Medicine, McGill University **Date:** 11-11-2023

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 1: Conflict of Interest Declaration for Clinician 1

Company	Check appropriate dollar range*			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
Novartis			x	
Amgen			x	
Sanofi		x		
HLS Therapeutics		x		
New Amsterdam	x			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 2

Name: Milan Gupta, MD

Position: Assistant Professor of Medicine, University of Toronto Date: 17-11-2023

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 2: Conflict of Interest Declaration for Clinician 2

Company	Check appropriate dollar range*			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
Amgen		X		

HLS		X		
New Amsterdam	X			
Novartis	X			
sanofi	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 3

Name: Jean Grégoire

Position: Associate Professor, Université de Montréal
Date: 20-11-2023

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 3: Conflict of Interest Declaration for Clinician 3

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Amgen			X	
HLS			X	
New Amsterdam	X			
Novartis			X	
Sanofi		X		

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 4

Name: Eva Lonn

Position: Professor of Medicine, McMaster University
Date: 23-11-2023

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 4: Conflict of Interest Declaration for Clinician 4

Company	Check appropriate dollar range*			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
Amgen		X		
HLS Therapeutics		X		
Novartis		X		
Servier	X			
Novo Nordisk	X			
New Amsterdam	X			
LIB Therapeutics		X		

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 5

Name: Robert Hegele MD FRCPC

Position: Staff Endocrinologist, London Health Sciences Centre Date: 20-11-2023

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 5

Company	Check appropriate dollar range*			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
Acasti	X			
Aegerion	X			
Akcea/Ionis	X			
Pfizer	X			
Regeneron	X			

Sanofi	X			
HLS Therapeutics		X		
Medison	X			
Novartis			X	
Amgen			X	

Declaration for Clinician 6

Name: David C. W. Lau, MD, PhD, FRCPC

Position: Professor Emeritus of Medicine, University of Calgary Date: 21-11-2023

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 6: Conflict of Interest Declaration for Clinician 6

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Amgen	X			
Novartis	X			
Bayer	X			
Novo Nordisk	X			
Boehringer-Ingelheim	X			
Viatris	X			
Zealand Pharma	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 6

Name: Jacques Genest MD

Position: Professor of Medicine, Cardiologist McGill University Health Center Date: 21 NOV 2023

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 6: Conflict of Interest Declaration for Clinician 6

No conflict of interest related to this topic.

Declaration for Clinician 7

Name: Ruth McPherson, MD, PhD, FRCPC

Position: Professor of Medicine, Director, Lipid Clinic, University of Ottawa Heart Institute

Date: 21/11/2023

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 7: Conflict of Interest Declaration for Clinician 7

Company	Check appropriate dollar range*			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
Amgen			x	
Novartis			x	

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 8

Name: Alexander Leung

Position: Associate Professor, Cumming School of Medicine, University of Calgary Date: November 21, 2023

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 8: Conflict of Interest Declaration for Clinician 8

Company	Check appropriate dollar range*			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
None				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 9

Name: Priya Manjoo

Position: Clinical Assistant Professor, University of British Columbia
Date: 21-11-2023

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 9: Conflict of Interest Declaration for Clinician 9

Company	Check appropriate dollar range*			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
NONE				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 10

Name: Gordon Francis

Position: Professor of Medicine, University of British Columbia
Date23-11-2023

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 10: Conflict of Interest Declaration for Clinician 10

	Check appropriate dollar range*

Company	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
None				

* Place an X in the appropriate dollar range cells for each company.

Clinician Group: University of Toronto faculty and clinicians at St Michael's Hospital who are actively involved in the treatment of patients with atherosclerotic cardiovascular disease and/or lipid disorders

CADTH Project Number: SR0821-000

Generic Drug Name (Brand Name): Repatha (Evolocumab)

Indication: For patients with recent acute coronary syndrome (ACS), who have LDL-C ≥ 1.8 mmol/L despite optimized lipid-lowering therapy (moderate-to-high intensity statin therapy, with or without ezetimibe).

Name of Clinician Group: University of Toronto faculty and clinicians at St Michael's Hospital who are actively involved in the treatment of patients with atherosclerotic cardiovascular disease and/or lipid disorders.

Author of Submission: Dr. Lawrence A. Leiter

1. About Your Clinician Group

We are all Faculty at the University of Toronto (https://www.utoronto.ca/about-u-of-t) and clinicians at St Michael's Hospital-Unity Health Toronto (https://unityhealth.to/locations/st-michaels-hospital/) who are actively involved in the treatment of patients with atherosclerotic cardiovascular disease (ASCVD) and/or lipid disorders to reduce their risk of having a (recurrent) vascular event.

2. Information Gathering

This submission is based on published data and our clinical experience.

3. Current Treatments and Treatment Goals

Cardiovascular disease remains a major cause of morbidity and mortality in Canada and lowering and maintaining an optimized low-density lipoprotein cholesterol (LDL-C) level is an essential component of our risk reduction strategies. Health behaviour modification and statins remain the initial treatment of patients with elevated LDL-C levels. Our current (2021) Canadian Cardiovascular Society (CCS) Guidelines recommend that in our patients with known atherosclerotic cardiovascular disease (ASCVD), non-statin agents be added if the LDL-C remains greater than 1.8 mmol/L despite being on maximally tolerated statin therapy. If the LDL-C is between 1.8 and 2.2 mmol/L, the CCS Guidelines recommend the addition of ezetimibe as the next step whereas if the LDL-C is greater than 2.2 mmol/L, it is recommended that a PCSK9 inhibitor (with or without ezetimibe) be added. When added to maximally tolerated statin therapy, the monoclonal antibodies to PCSK9, evolocumab and alirocumab, lower LDL-C by an additional 60% and have been shown in large outcome studies to significantly reduce the risk of cardiovascular morbidity and mortality, with excellent safety and tolerability profiles.

In the FOURIER trial (Sabatine M et al. NEJM 2017; 376:1713) the largest completed trial with a lipid-lowering agent, 27,564 patients with stable ASCVD were randomly assigned to either evolocumab or placebo. In this event-driven trial with a median follow-up duration of 2.2 years, those patients receiving evolocumab had a 15% relative risk reduction (RRR) in the primary endpoint of major adverse cardiovascular events (MACE: cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization) and a 20% RRR in the key secondary MACE endpoint (cardiovascular death, myocardial infarction, or stroke).

With respect to safety, evolocumab was essentially indistinguishable from placebo with the only more frequent side effect being a small increase in local injection site reactions, that rarely led to treatment discontinuation. In a subsequent analysis focusing on the 5711 patients with a recent myocardial infarction (i.e., within 12 months of randomization) (Gencer B et al. JAMA Cardiol 2020; 5:952), the

RRR was 19% for the primary endpoint and 25% for the secondary endpoint, with absolute risk reductions of 3.7% and 3.2% over 2.2 years of follow-up. In a subsequent open-label extension of the original trial (FOURIER-OLE) whereby 6635 patients received open-label evolocumab for an additional 5 years, those participants originally randomized to evolocumab had an additional 15% RRR in MACE, a 20% RRR in the secondary MACE endpoint and, importantly, a 20% RRR in cardiovascular mortality (O'Donoghue ML et al. Circulation 2022:146:1109-19). The average LDL-C reduction of about 60% was sustained over the additional 5 years of follow-up and no new safety issues emerged. Consistent with the findings in the overall trial population during the active placebo comparison, the patients with the lowest LDL-C levels experienced the lowest cardiovascular event rates. This study highlighted the importance of early initiation of PCKS9 inhibitors (e.g., within the first 12 months of an acute coronary event [ACS]) in appropriate patients since "…earlier initiation of PCSK9 inhibitors provides a degree of risk mitigation that cannot be achieved when therapy is delayed." (Shapiro MD. Circulation 2022:146:1120-22)

Based upon the Gencer et al. subgroup analysis and the ODYSSEY OUTCOMES trial, the 2021 CCS Lipid Guidelines now include "recent (hospital-52 weeks) ACS" among the groups of "secondary prevention patients shown to derive the largest benefit from intensification of statin therapy with the additional use of a PCSK9 inhibitor.

4. Treatment Gaps (unmet needs)

Considering the treatment goals in Section 3, please describe goals (needs) that are not being met by currently available treatments.

A number of recent Canadian population-based, real-world studies have demonstrated that many patients who are at high cardiovascular risk continue to have LDL-C levels well above the CCS Guidelines recommended LDL-C threshold of 1.8 mmol/L, including those with a recent ACS (Sud M et al. J Am Coll Cardiol 2020;76:1440-50; Sarak B et al. Circulation: Cardiovascular Quality and Outcomes 2021;14:e006646). This is a result of multiple factors including insufficient LDL-C lowering with statins (with or without ezetimibe), statin-associated side effects, suboptimal medication adherence, and treatment inertia. The addition of PCSK9 monoclonal antibodies is an exceptionally well-tolerated and potent tool that can bring the LDL-C levels below threshold in most of the estimated 30-40% of patients who, despite maximally tolerated statin (with or without ezetimibe), are unable to achieve an optimal LDL-C.

For example, in our clinical practice, we see a significant number of individuals with high cardiovascular risk who are unable to achieve targe LDL-C due to statin-associated adverse effects such as myalgias, muscle weakness, significant elevations in creatinine kinases levels, and (less commonly) increases in liver enzyme levels. Despite our persistent efforts to reintroduce statins at lower doses with the goal of achieving a compromise between side effects and cardiovascular protection, the "maximally tolerated" dose is often a very low dose that is insufficient to achieve the recommended LDL-C levels. Ezetimibe (a second-line treatment) is better tolerated than statins, but much less potent, so many patients end up living long-term with suboptimal LDL-C levels which in turn results in them being exposed to ongoing higher cardiovascular risk. In our experience, patients who able to gain access to the recommended PCSK9 monoclonal antibody treatments experience an immediate and sustained LDL-C reduction well below threshold, with usually no side effects, apart from occasional injection site reactions.

Many patients in whom PCSK9 inhibitors would be appropriate are not receiving these agents, with cost and access identified as major barriers. These drugs are not covered for public reimbursement in Canada for patients with ASCVD, except in those who have familial hypercholesterolemia. The coverage of a PCKS9 inhibitor like evolocumab in post-ACS patients would facilitate improved access, help to get the LDL-C of more of these patients with high cardiovascular risk to levels below the recommended threshold values, and would significantly reduce MACE, including myocardial (re-)infarction, ischemic stroke, the need for coronary revascularization (percutaneous coronary intervention/stenting and coronary artery bypass surgery), and cardiovascular death.

5. Place in Therapy

How would the drug under review fit into the current treatment paradigm?

Evolocumab is a PCSK9 inhibitor that has been approved in Canada since 2015 for the reduction of LDL-C 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, as an adjunct to diet, alone or in combination with non-statin lipid-lowering therapies, in patients for whom a statin is contraindicated.

Following the publication of the results of the FOURIER trial, the indication for evolocumab was broadened to also include it as an adjunct to diet and standard of care therapy (including moderate- to high-intensity statin therapy alone or in combination with other lipid-lowering therapy), to reduce the risk of myocardial infarction, stroke, and coronary revascularization in adult patients with ASCVD by further lowering LDL-C levels.

The mechanism of action underlying the benefits of evolocumab is complementary to those of other lipid-lowering drugs, including statins and ezetimibe, and thus it is recommended to be used in patients with ASCVD whose LDL-C levels remain elevated despite the use of maximally tolerated dose of a high-intensity statin such as atorvastatin or rosuvastatin, with or without ezetimibe. There is also clinical trial evidence for early LDL-C lowering efficacy of evolocumab and safety immediately post-ACS in the EVOPACS (Koskinas KC et al. JACC 2019; 74:2452) and EVACS (Leucker TM et al. Circulation 2020; 142:419) studies.

At the present time, lack of access to PCSK9 inhibitors has resulted in many high-risk post-ACS Canadian patients unable to attain current LDL-C targets/thresholds and thus being denied the potential benefits of optimized LDL-C levels and reduced risk for recurrent cardiovascular events and revascularization procedures.

Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

The appropriate patients would be easily identified by specialists and primary care physicians as those who are within one year of hospitalization for an ACS event whose LDL-C remains above the guideline-recommended threshold of 1.8 mmol/L despite being on maximally tolerated statin dose, with or without ezetimibe.

What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

An appropriate response would be identified by a simple follow-up LDL-C blood test 4-8 weeks after treatment initiation to determine if the patient's LDL-C has decreased appropriately (typically about a 60% reduction) below the CCS Guidelines-recommended threshold of 1.8 mmol/L.

What factors should be considered when deciding to discontinue treatment with the drug under review?

Lipid-lowering medication is typically continued indefinitely unless there are adverse events or lack of adequate response (both of which are rare with evolocumab). Clinical trials have indicated that the longer duration that LDL-C is lowered, the greater the cardiovascular benefit.

What settings are appropriate for treatment with [drug under review]? Is a specialist required to diagnose, treat, and monitor patients who might receive [drug under review]?

The medication is easily self-administered by the patient every 2 to 4 weeks (depending on the dose) and can be done in any setting (most typically at home). Any physician (such as primary care physicians or specialists) can identify the appropriate patient (as above), prescribe the medication, and monitor treatment effects with routine lipid bloodwork.

6. Additional Information

No

7. Conflict of Interest Declarations

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict of interest declaration is required for participation.

Declarations made do not negate or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

1. Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

No

2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

No

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. **Please note that this is required for each clinician who contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

Declaration for Clinician 1

Name: Lawrence A. Leiter

Position: Director, Lipid Clinic, St. Michael's Hospital, Unity Health Toronto; Professor of Medicine and Nutritional Sciences, University of Toronto

Date: 01-11-2023

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 1: Conflict of Interest Declaration for Clinician 1

Company	Check appropriate dollar range*			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
Amgen			X (for consulting and Executive Committee activities in the VESALIUS Trial)	

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 2

Name: Shaun G. Goodman

Position: Associate Head of the Division of Cardiology, St. Michael's Hospital, Unity Health Toronto; Professor of Medicine, University of Toronto

Date: 12-11-2023

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 2: Conflict of Interest Declaration for Clinician 2

Company	Check appropriate dollar range*			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
Amgen			X (for consulting — including for a presentation during a pre-submission meeting with CADTH-- and Steering Committee activities in the PROgram To Evaluate Cardiovascular disease Treatment in ASCVD [PROTECT-ASCVD] Initiative	
			(2023-present) and Cardiovascular Multi-country OBservational Investigation of the Use of pcSk9 inhibitors [CV MOBIUS] (2019-2020)	

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 3

Name: Alice Y. Y. Cheng

Position: Endocrinologist, St. Michael's Hospital, Unity Health Toronto; Associate Professor, University of Toronto

Date: 13-11-2023

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 3: Conflict of Interest Declaration for Clinician 3

Company	Check appropriate dollar range*			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
Amgen	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 4

Name: Beth Abramson

Position: Staff Cardiologist, St. Michael's Hospital, Unity Health Toronto; Paul Albrechtsen Professor in Cardiac Prevention and Women's Health, and Associate Professor of Medicine, University of Toronto

Date: 14/11/2023

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 4: Conflict of Interest Declaration for Clinician 4

Company	Check appropriate dollar range*			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
Amgen		X (Consulting and CME presentations)		

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 5

Name: John L. Sievenpiper

Position: Staff Physician, St. Michael's Hospital, Unity Health Toronto; Professor of Nutritional Sciences and Medicine, University of Toronto

Date: 13-11-2023

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 5

Company	Check appropriate dollar range*			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
Amgen	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 6

Name: Linda Wang

Position: Staff Endocrinologist, St. Michael's Hospital, Unity Health Toronto

Date: 16-11-2023

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 6

Company	Check appropriate dollar range*			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
Add or remove rows as required	X (None)			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 7

Name: Kim A. Connelly

Position: Executive Director, Keenan Research Centre for Biomedical Science; Division Head of Cardiology, St. Michael's Hospital, Unity Health Toronto; Associate Professor of Medicine and Physiology, University of Toronto Date: 17-11-2023

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 4: Conflict of Interest Declaration for Clinician 7

Company	Check appropriate dollar range*			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
Amgen	X - honoraria			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 8

Name: Subodh Verma

Position: Staff Cardiac Surgeon, St. Michael's Hospital, Unity Health Toronto; Professor of Surgery, and Pharmacology and Toxicology, University of Toronto

Date: 17-11-2023

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 8

Company	Check appropriate dollar range*			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
Amgen			X (for serving on the steering committee of the VESALIUS-CV Trial; speaking; consulting; patient recruitment for Amgen trials including VESALIUS and OCEAN)	

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 9

Name: Bobby Yanagawa

Position: Division Head of Cardiac Surgery, St. Michael's Hospital, Unity Health Toronto; Associate Professor of Surgery, and Pharmacology and Toxicology, University of Toronto

Date: 13-11-2023

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 9

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Add or remove rows as required	X (None)			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 10

Name: Dominic Ng

Position: Staff Endocrinologist, St. Michael's Hospital, Unity Health Toronto; Associate Professor of Medicine, University of Toronto

Date: 17-11-2023

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 10

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Amgen	X (speaker fees)			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 11

Name: Cynthia T. Luk

Position: Staff Endocrinologist; St. Michael's Hospital, Unity Health Toronto; Assistant Professor of Medicine, University of Toronto

Date: 18-11-2023

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 11

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Add or remove rows as required	X (None)			

* Place an X in the appropriate dollar range cells for each company.

Clinician Group: University of British Columbia and Vancouver General Hospital/St. Paul's Hospital Cardiac Intensive Care Unit (CICU) attending physicians

CADTH Project Number: SR0821-000

Generic Drug Name (Brand Name): Evolocumab

Indication: Patients with recent acute coronary syndrome (ACS), who have LDL-C ≥ 1.8 mmol/L despite optimized lipid-lowering therapy (moderate-to-high intensity statin therapy, with or without ezetimibe)

Name of Clinician Group: University of British Columbia and Vancouver General Hospital/St. Paul's Hospital Cardiac Intensive Care Unit (CICU) attending physicians

Author of Submission: Christopher Fordyce, MD, MHS, MSc, FRCPC

1. About Your Clinician Group

Please describe the purpose of your organization. Include a link to your website (if applicable).

This is a group of University of British Columbia-affiliated cardiologists who attend in the Cardiac Intensive Care Units (CICUs) of Vancouver General Hospital (VGH) and St. Paul's Hospital (SPH) within the Vancouver Coastal Health Authority (VCHA).

VCHA serves 1.25 million of British Columbia's population of five million (approximately one in four) who live in a geographic area of 58,560 square km that includes 12 municipalities, four regional districts and 14 Aboriginal communities. VCHA comprises 13 hospitals, of which VGH and SPH have invasive coronary angiography/percutaneous coronary intervention (PCI) capability. VGH and SPH comprise two of five PCI centers in British Columbia, and routinely accept acute coronary syndrome (ACS) patients via transfer from other health authorities without PCI or CICU facilities, including Northern Health Authority.

The CICU cardiology group is responsible for the initial diagnostic workup and treatment of acutely ill cardiac patients, including across the spectrum of ACS.

The vast majority of CICU physicians also follow-up their patients longitudinally post-discharge in the ambulatory setting to optimize secondary prevention targets, including LDL-C.

2. Information Gathering

Please describe how you gathered the information included in the submission.

The CICU cardiology group is well versed in randomized clinical trials and contemporary guidelines recommending the use of PCSK-9 inhibitors, including evolocumab, as an important adjunct to achieve LDL-C levels < 1.8 among ACS patients. In a subgroup analysis of the FOURIER trial (Sabatine, NEJM 2018), among patients with more recent ACS, those randomized to evolocumab had a significantly greater reduction in major adverse cardiovascular events (MACE) compared to those without a recent ACS (Gencer, JAMA Cardiology 2020). The EVOPACS (Koskinas, JACC 2019) trial demonstrated a more rapid reduction in LDL, as well as safety, among ACS patients randomized to evolocumab during their index admission for ACS, compared to usual care.

The CICU cardiology group are aware of high-quality registry studies demonstrating that a significant proportion of ACS patients do not achieve LDL-C targets, often as a result of access and cost, which has been associated with recurrent MACE.

3. Current Treatments and Treatment Goals

Please describe the current treatment paradigm for the disease.

Focus on the Canadian context.

Please include drug and non-drug treatments.

Drugs without Health Canada approval for use in the management of the indication of interest may be relevant if they are routinely used in Canadian clinical practice. Treatments available through special access programs are relevant. Are such treatments supported by clinical practice guidelines?

Do current treatments modify the underlying disease mechanism? Target symptoms?

Examples: *Prolong life, delay disease progression, improve lung function, prevent the need for organ transplant, prevent infection or transmission of disease, reduce loss of cognition, reduce the severity of symptoms, minimize adverse effects, improve health-related quality of life, increase the ability to maintain employment, maintain independence, reduce burden on caregivers.*

It is well documented that among ASCVD patients, the lower the LDL, the lower the risk of adverse events (Wright, JACC 2016). Of all ASCVD patients, those discharged with ACS represent the highest risk patients, with the risk of a MACE exceeding 10% in the first-year post discharge (Wallentin, NEJM 2009)

Standard treatments for ACS include statins and ezetimibe. However, it is estimated that 2 in 5 patients post-ACS do not achieve the current LDL-C target of < 1.8, even when taking these medications regularly (Wiviott, JACC 2015). Half of ASCVD patients receiving PCI (ACS and elective indications) do not achieve an LDL-C < 1.8. (Harris, Eur J Prev Card 2021). Conversely, more rapid and greater LDL lowering post ACS is associated with significantly improved outcomes (Schuber, EHJ 2021)

4. Treatment Gaps (unmet needs)

4.1. Considering the treatment goals in Section 3, please describe goals (needs) that are not being met by currently available treatments.

Please describe goals (needs) that are not being met by currently available treatments. Examples of unmet needs:

- *Not all patients respond to available treatments*
- *Patients become refractory to current treatment options*
- *No treatments are available to reverse the course of disease*
- *No treatments are available to address key outcomes*
- *Treatments are needed that are better tolerated*
- *Treatments are needed to improve compliance*
- *Formulations are needed to improve convenience*

Please describe limitations associated with current treatments (e.g., adverse events, administration, etc., if applicable).

Evolocumab is only funded in British Columbia for the indication of familial hypercholesteremia (FH) among patients who do not achieve optimal LDL-C levels on maximally tolerated statins and ezetimibe.

The issue is that FH patients comprise a small proportion of ACS patients in general. Therefore, a risk-treatment paradox exists such that the highest risk ASCVD patients, those discharged post ACS, do not have public access to evolocumab.

5. Place in Therapy

5.1. How would the drug under review fit into the current treatment paradigm?

Is there a mechanism of action that would complement other available treatments, and would it be added to other treatments?

Is the drug under review the first treatment approved that will address the underlying disease process rather than being a symptomatic management therapy?

Would the drug under review be used as a first-line treatment, in combination with other treatments, or as a later (or last) line of treatment?

Would the drug under review be reserved for patients who are intolerant to other treatments or in whom other treatments are contraindicated?

Is the drug under review expected to cause a shift in the current treatment paradigm?

Please indicate whether or not it would be appropriate to recommend that patients try other treatments before initiating treatment with drug under review. Please provide a rationale for your perspective.

Evolocumab is generally an adjunct to maximally tolerated statins +/- ezetimibe to achieve LDL-C targets. However, many patients will not tolerate statins and others cannot achieve target LDL-C on those medications (above).

5.2. Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

Which patients are most likely to respond to treatment with drug under review?

Which patients are most in need of an intervention?

Would this differ based on any disease characteristics (e.g., presence or absence of certain symptoms, stage of disease)?

How would patients best suited for treatment with drug under review be identified (e.g., clinician examination/judgement, laboratory tests (specify), diagnostic tools (specify))

Are there any issues related to diagnosis?

Is a companion diagnostic test required?

Is it likely that misdiagnosis occurs in clinical practice (e.g., underdiagnosis)?

Is it possible to identify those patients who are most likely to exhibit a response to treatment with drug under review?

Although all ASCVD patients should be treated to target LDL-C < 1.8, ACS patients remain at the highest risk of MACE (above). They are readily identifiable at discharge from hospital. Most patients on evolocumab exhibit a robust response to the medication, with an approximate 50% reduction in LDL-C on top of statins +/- ezetimibe.

5.3 What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

Are outcomes used in clinical practice aligned with the outcomes typically used in clinical trials?

What would be considered a clinically meaningful response to treatment? Consider the magnitude of the response to treatment. Is this likely to vary across physicians?

Examples: improved survival; reduction in the frequency/severity of symptoms (provide specifics regarding changes in frequency, severity, etc.); attainment of major motor milestones; ability to perform activities of daily living; improvement of symptoms; and stabilization (no deterioration) of symptoms.

Achieving an LDL-C < 1.8 on therapy is a practical and reasonable target, that could be performed between 2 to 12 months following initiation. However, once a patient responds to evolocumab, it is general unnecessary to continually evaluate efficacy in the long-term as there is a dramatic and sustained reduction of LDL-C lowering with PCSK-9 inhibition..

5.4 What factors should be considered when deciding to discontinue treatment with the drug under review?

Examples: disease progression (specify, e.g. loss of lower limb mobility); certain adverse events occur (specify type/frequency/severity); or additional treatment becomes necessary (specify).

In the clinical trials and in registry data, evolocumab is well tolerated and there is therefore limited reason to discontinue the medication in the vast majority of patients.

5.5 What settings are appropriate for treatment with [drug under review]? Is a specialist required to diagnose, treat, and monitor patients who might receive [drug under review]?

Examples: Community setting, hospital (outpatient clinic), specialty clinic

If a specialist is required, which specialties would be relevant?

The medication is easy to administer with very few side effects, and does not require any specialized monitoring apart from initial lipid levels (above). This should be available for primary care practitioners to prescribe.

6. Additional Information

Is there any additional information you feel is pertinent to this review?

As above, public reimbursement in Canada for any PCSK-9 inhibitor is only for FH patients. Some patients with ASCVD have 3rd party insurance. However, there are a significant proportion of ACS patients who have neither FH or 3rd party coverage and who do not have access to these life saving medications. A CADTH recommendation for evolocumab public reimbursement for ACS will resolve the inequity that currently exist and improve outcomes, which would be expected to reduce healthcare costs in the long-run.

7. Conflict of Interest Declarations

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

1. Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

   No.

2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

   No.

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. **Please note that this is required for <u>each clinician</u> who contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

Declaration for Clinician 1

Name: Christopher Fordyce, MD, MHS, MSc

Position: Associate Professor, UBC Division of Cardiology, and Director and attending physician, VGH Cardiac Intensive Care Unit

Date: 18-11-2023

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 1: Conflict of Interest Declaration for Clinician 1

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Bayer	x			
Novo Nordisk		x		
Boehringer Ingelheim		x		
Sanofi		x		
Novartis	x			
New Amsterdam	x			
HLS Therapeutics	x			

* Place an X in the appropriate dollar range cells for each company.

Research grants from: Amgen, Novartis, Bayer

Declaration for Clinician 2

Name: Graham Wong, MD, MPH

Position: Cardiologist and VGH CICU attending physician, Professor, UBC Division of Cardiology

Date: <24-11-2023>

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 2: Conflict of Interest Declaration for Clinician 2

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Add company name	None			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 3

Name: Ken Gin, MD

Position: Cardiologist and VGH CICU attending physician, Professor, UBC Division of Cardiology

Date: <23-11-2023>

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 3: Conflict of Interest Declaration for Clinician 3

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Add company name	None			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 4

Name: Tara Sedlak, MD, MBA

Position: Cardiologist and VGH CICU attending physician, Associate Professor, UBC Division of Cardiology

Date: <20-11-2023>

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 4: Conflict of Interest Declaration for Clinician 4

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Novartis	x			
Amgen	x			
HLS therapeutics	x			
Pfizer	x			
NovoNordisk		x		
Pendopharm	x			
Bayer	x			
BI Lilly	x			
KYE Pharmaceuticals		x		

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 5

Name: Nathan Brunner, MD

Position: Cardiologist and VGH CICU attending physician, Associate Professor, UBC Division of Cardiology

Date: <20-11-2023>

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 5

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Janssen Pharmaceuticals	x			
Merck Pharmaceuticals	x			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 6

Name: Michael Tsang, MD

Position: Cardiologist and VGH CICU attending physician, Associate Professor, UBC Division of Cardiology

Date: <24-11-2023>

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 6

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**

Add company name	None			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 7

Name: Thomas Roston, MD, PhD

Position: Cardiologist and VGH/SPH CICU attending physician, Assistant Professor, UBC Division of Cardiology

Date: <19-11-2023>

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 7

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Cardurion Pharmaceuticals	x			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 8

Name: Krishnan Ramanathan, MB, CHB

Position: Cardiologist and VGH/SPH CICU attending physician, Professor, UBC Division of Cardiology

Date: <24-11-2023>

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 8

Company	Check appropriate dollar range*			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
Add company name	None			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 9

Name: Mustafa Toma, MD, MS

Position: Associate Professor, UBC Division of Cardiology, and Director and attending physician, SPH Cardiac Intensive Care Unit

Date: <20-11-2023>

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 9

Company	Check appropriate dollar range*			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
Novartis	x			
Servier	x			
Novo Nordisk	x			
AstraZeneca	x			
Boehringer Ingelheim	x			

in the appropriate dollar range cells for each company.

Declaration for Clinician 10

Name: Kendeep Kaila, MD

Position: Cardiologist and SPH CICU attending physician, Assistant Professor, UBC Division of Cardiology

Date: <20-11-2023>

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 10

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Add company name	None			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 11

Name: Sean Virani, MD, MSc, MPH

Position: Cardiologist and SPH CICU attending physician, Associate Professor, UBC Division of Cardiology

Date: <20-11-2023>

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 11

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**

Add company name	None			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 12

Name: Marc Deyell, MD, MSc

Position: Cardiologist and SPH CICU attending physician, Associate Professor, UBC Division of Cardiology

Date: <18-11-2023>

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 12

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Biosense Webster		x		
Kardium		x		
Boehringer Ingelheim	x			
Servier	x			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 13

Name: Kevin Ong, MD

Position: Cardiologist and SPH CICU attending physician, Associate Professor, UBC Division of Cardiology

Date: <20-11-2023 >

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 513

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Bristol Myers Squibb			x	

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 14

Name: Jasmine Grewal, MD

Position: Cardiologist and SPH CICU attending physician, Professor, UBC Division of Cardiology

Date: <20-11-2023 >

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 14

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Add company name	None			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 15

Name: Robert Boone, MD, MSc

Position: Cardiologist and SPH CICU attending physician, Assistant Professor, UBC Division of Cardiology

Date: < 20-11-2023 >

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 15

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Add company name	None			

* Place an X in the appropriate dollar range cells for each company.