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CADTH Reimbursement Recommendation

Evinacumab (Evkeeza)

Indication: As an adjunct to diet and other low-density lipoprotein cholesterol (LDL-C) lowering therapies for the treatment of adult and pediatric patients aged 5 years and older with homozygous familial hypercholesterolemia (HoFH).

Sponsor: Ultragenyx Pharmaceutical Inc.

Final recommendation: Reimburse with conditions

Summary

What Is the CADTH Reimbursement Recommendation for Evkeeza?

CADTH recommends that Evkeeza be reimbursed by public drug plans as an adjunct to diet and other low-density lipoprotein cholesterol (LDL-C)–lowering therapies for the treatment of adult and pediatric patients aged 5 years and older with homozygous familial hypercholesterolemia (HoFH) if certain conditions are met.

Which Patients Are Eligible for Coverage?

Evkeeza should only be covered to treat patients aged 5 years and older with a diagnosis of HoFH and extremely high levels of LDL-C (sometimes referred to as *bad cholesterol*) despite receiving other cholesterol-lowering treatments.

What Are the Conditions for Reimbursement?

Evkeeza should only be reimbursed if prescribed by specialists with experience in managing HoFH and if the cost of Evkeeza is reduced.
Evkeeza may only be prescribed for 24 weeks the first time it is used.
To continue treatment with Evkeeza longer than 6 months, the treating physician must provide proof that the patient is responding to treatment, defined as reduction in LDL-C levels.

Why Did CADTH Make This Recommendation?

- Evidence from 2 clinical trials (the ELIPSE and CL-17100 trials) demonstrated that treatment with Evkeeza lowered LDL-C by 49% over 6 months in patients with HoFH when added to other cholesterol-lowering treatments.
- Although treatments are available, substantial morbidity and mortality still exists for patients with HoFH. Evkeeza may meet some needs that are important to patients, as it is another treatment option that reduces LDL-C levels, which is an important outcome for patients with HoFH.
- Based on CADTH's assessment of the health economic evidence, Evkeeza does not represent good value to the health care system at the public list price. A price reduction is therefore required.
- Based on public list prices, Evkeeza is estimated to cost the public drug plans approximately $55 million over the next 3 years.

Summary

Additional Information

What Is HoFH?

HoFH is a rare genetic disease that causes extremely high levels of LDL-C. Atherosclerotic cardiovascular disease (ASCVD) occurs when LDL-C builds up inside the arteries, leading to hardening and narrowing of arteries and resulting in reduced blood flow. Severe outcomes of ASCVD because of HoFH may include heart attack, stroke, or death. HoFH is estimated to occur in 1 in every 250,000 people globally and affects approximately 80 people in Canada.

Unmet Needs in HoFH

Statins and ezetimibe are the standard treatments for lowering cholesterol, but these alone may not help most patients with HoFH. Other options — including proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors — are not publicly funded, which reduces the treatment options available to all patients, and while effective, the removal of LDL-C from the blood (LDL apheresis) is only temporary and time-consuming. There is a need for more treatments in HoFH that lower LDL-C, reduce the need for or frequency of LDL apheresis, and reduce cardiovascular morbidity and death.

How Much Does Evkeeza Cost?

Treatment with Evkeeza is expected to cost the public drug plans approximately $460,839 per year, assuming a patient weight of 70 kg.

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that evinacumab be reimbursed as an adjunct to diet and other low-density lipoprotein cholesterol (LDL-C)–lowering therapies for the treatment of adult and pediatric patients aged 5 years and older with homozygous familial hypercholesterolemia (HoFH), only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

HoFH is a rare genetic disease in which atherosclerotic cardiovascular disease (ASCVD) occurs at a very young age, progressing aggressively throughout life, and can result in premature death. Although treatments are available, CDEC emphasized that substantial morbidity and mortality still exists, highlighting a significant unmet need for patients with HoFH. While there was insufficient evidence to evaluate the effect of evinacumab on the reduction in cardiovascular (CV) morbidity and mortality, CDEC recognized that reducing LDL-C levels is an important outcome in patients with HoFH, and there is a relationship between LDL-C levels and CV morbidity and mortality in this patient population.

One phase III, double-blind randomized controlled trial (RCT) (the ELIPSE trial; N = 65) demonstrated that, compared with placebo, evinacumab 15 mg/kg every 4 weeks resulted in added clinical benefit for patients aged 12 years and older with HoFH in reducing plasma LDL-C. In the ELIPSE trial, evinacumab resulted in a statistically significant and clinically meaningful percent reduction in LDL-C from baseline at 24-weeks compared to placebo (least squares mean difference [LSMD] = −49.0%; 95% confidence interval [CI], −65.0 to −33.1). In addition, evinacumab was associated with a clinically meaningful reduction from baseline in absolute LDL-C and apolipoprotein B (Apo B), and a clinically meaningful proportion of patients with a percent reduction in LDL-C of 30% or more. Results from 1 single-arm, open-label study (the CL-17100 trial; N = 20), which enrolled patients aged 5 to 11 years with HoFH, were consistent with those observed in the ELIPSE trial for the outcomes of percent and absolute change from baseline in LDL-C.

Patients identified a need for treatment options that reliably and consistently control LDL-C at normal or near-normal levels, reduce the frequency and need for apheresis, and reduce CV events. Based on the evidence reviewed, CDEC concluded that evinacumab meets the need of reducing LDL-C, but there was insufficient evidence to evaluate the effect of evinacumab on the reduction in the frequency of apheresis or CV morbidity and mortality.

Using the sponsor-submitted price for evinacumab and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) for evinacumab was $8,392,585 per quality-adjusted life-year (QALY) gained, compared with standard of care. At this ICER, evinacumab is not cost-effective at a $50,000 per QALY willingness-to-pay threshold for patients aged 5 years and older with HoFH. A price reduction is required for evinacumab to be considered cost-effective at a $50,000 per QALY gained threshold.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Adult and pediatric patients aged 5 years and older with a clinically or genetically confirmed diagnosis of HoFH, defined as: 1.1. Clinical criteria: 1.1.1. Untreated TC > 12.93 mmol/L and TGs < 3.39 mmol/L, and 1.1.2. Both parents with documented TC > 6.47 mmol/L, indicative of HeFH, or patient with cutaneous or tendinous xanthoma before the age of 10 years 1.2. Genetic criteria: 1.2.1. Documented functional mutation or mutations in both LDLR alleles, or 1.2.2. Documented homozygous or compound heterozygous mutations in Apo B or PCSK9, or LDLRAP1, or at least 2 such variants at different loci	The ELIPSE trial enrolled patients with HoFH aged 12 years and older, and the supportive CL-17100 study enrolled patients with HoFH between the ages of 5 and 11 years. Patients in the ELIPSE and CL-17100 trials had either clinical or genetic confirmation of HoFH, defined as: Clinical criteria: • Untreated TC > 12.93 mmol/L and TGs < 3.39 mmol/L, and • Both parents with documented TC > 6.47 mmol/L, indicative of HeFH, or patient with cutaneous or tendinous xanthoma before the age of 10 years Genetic criteria: • Documented functional mutation or mutations in both LDLR alleles, or • Documented homozygous or compound heterozygous mutations in Apo B or PCSK9, or LDLRAP1, or at least 2 such variants at different loci	–
2. Patients must have elevated LDL-C despite an adequate trial of other accessible lipid-lowering therapies; "elevated LDL-C" is defined as LDL-C greater than 1.8 mmol/L at baseline for adult patients and greater than 3.4 mmol/L for children.	Patients in the ELIPSE trial were required to have an LDL-C level greater than 1.8 mmol/L at the screening visit, while patients in the CL-17100 trial were required to have an LDL-C level greater than 3.4 mmol/L at the screening visit while receiving a stable dose of maximally tolerated therapy.	CDEC noted that patients in the included trials were required to be receiving stable lipid-lowering therapy at the maximum dose that did not cause intolerable side effects. In general, most patients had a lipid-lowering therapy background consisting of statins, ezetimibe, and PCSK9 inhibitors. CDEC highlighted that intolerance to a prerequisite lipid-lowering therapy should not preclude access to evinacumab. CDEC noted that evinacumab monotherapy may be considered in patients who have contraindications to or are unable to tolerate other accessible lipid-lowering therapies. The clinical experts noted to CDEC that TG elevations are not typically present in patients with HoFH, and when they are, LDL-C levels are generally underestimated. If the TG is between 4.5 mmol/L and 9

Reimbursement condition	Reason	Implementation guidance
		mmol/L, it would be reasonable to consider recalculation of the LDL-C using the Martin-Hopkins equation.
3. The physician must provide the baseline LDL-C when the initial request for reimbursement occurs after all other treatment options of lipid-lowering therapies have been exhausted.	Patients in the CL-17100 study were required to have an LDL-C level greater than 3.4 mmol/L at screening, while patients in the ELIPSE trial were required to have an LDL-C level greater than 1.8 mmol/L at screening.	—
4. The maximum duration of initial authorization is 24 weeks.	The primary outcome of the ELIPSE trial was the change from baseline in LDL-C, which was assessed at week 24. This is consistent with input from clinical experts that patients with HoFH are seen as often as every 3 months, and at minimum every 6 months.	—
Renewal		
5. For renewal after initial authorization and subsequent renewals, the physician must provide proof of beneficial clinical effect when requesting continuation of reimbursement, defined as reduction in LDL-C from baseline that is considered clinically beneficial by the treating physician.	The proportion of patients with a 30% reduction in LDL-C was a secondary end point of the ELIPSE trial. The clinical experts considered a 20% reduction in LDL-C to be clinically meaningful in patients with HoFH.	According to the 2023 European Atherosclerotic Society guidelines, it is recommended that adult patients (≥ 18 years) with HoFH maintain an LDL-C level of less than 1.8 mmol/L, and less than 1.4 mmol/L in patients with additional ASCVD risk factors such as elevated lipoprotein(a) or diabetes mellitus, or those with established ASCVD. These guidelines also specify the target LDL-C level to be < 3 mmol/L in children. However, the guidelines acknowledge that these goals are based on expert recommendations and have not been tested in clinical trials, and that achieving these goals may be challenging in real-world practice. For patients able to access pheresis treatments, distinguishing the specific effect of evinacumab on lipid levels becomes difficult and must rely on expert opinion.
6. Subsequent renewals should be assessed annually.	Annual assessments will help ensure the treatment is used for those benefiting from the therapy and would reduce the risk of unnecessary treatment.	—
Prescribing		
7. Evinacumab must be prescribed by specialists with qualifications and experience in the diagnosis and management of HoFH (e.g.,	Accurate diagnosis and management of patients with HoFH is important to ensure that evinacumab is prescribed to appropriate patients.	Patients may be comanaged after initiation of therapy with prescribers who work at a site with IV infusion facilities.

Reimbursement condition	Reason	Implementation guidance
[pediatric] endocrinologists, cardiologists, lipidologists).		
Pricing		
8. A reduction in price.	At the submitted price, the ICER of evinacumab is $8,392,585 per QALY gained when compared with standard of care. A price reduction of 98% would be required for evinacumab to achieve an ICER of $50,000 per QALY gained compared to standard of care.	—

AE = adverse event; Apo B = apolipoprotein B; ASCVD = atherosclerotic cardiovascular disease; CDEC = CADTH Canadian Drug Expert Committee; HeFH = heterozygous familial hypercholesterolemia; HoFH = homozygous familial hypercholesterolemia; ICER = incremental cost-effectiveness ratio; LDL-C = low-density lipoprotein cholesterol; LDLR = low-density lipoprotein receptor; LDLRAP1 = low-density lipoprotein receptor adaptor protein 1; MTD = maximally tolerated dose; PCSK9 = proprotein convertase subtilisin/kexin type 9; QALY = quality-adjusted life-year; TC = total cholesterol; TG = triglycerides.

Discussion Points

- A request for minor reconsideration of the initial draft recommendation for evinacumab was received from the drug plans. The reconsideration included issues related to clarifications on the definition of elevated LDL-C in patients with HoFH who are already receiving treatment with current standard of care, what an adequate trial of standard of care is, accessibility of PCSK9 inhibitors as a standard of care therapy, and specific LDL-C thresholds for renewal eligibility. During the minor reconsideration discussion, a subpanel of the committee discussed the issues raised by the drug plans and discussed each of the concerns identified by the drug plans in their request for reconsideration. CDEC also discussed feedback from the sponsor and the clinical experts on the initial draft recommendation.
- There was uncertainty with the clinical evidence; therefore, the committee deliberated on evinacumab considering the criteria for significant unmet need that are described in section 9.3.1 of the Procedures for CADTH Reimbursement Reviews. Considering the rarity and severity of the condition, and the absence of clinically effective alternatives, the committee concluded that the available evidence reasonably suggests that evinacumab could substantially reduce LDL-C from baseline.
- In patients with HoFH, markedly high plasma LDL-C levels from birth can result in early CV complications due to accelerated development of ASCVD and premature death. CDEC considered the rarity of the disease and recognized the unmet need in patients with HoFH, as there remains significant morbidity and mortality despite the currently available standard of care therapies (i.e., statins, ezetimibe, and PCSK9 inhibitors), as well as LDL apheresis, and in some patients, lomitapide.
- The included studies demonstrated that evinacumab results in a clinically meaningful reduction in plasma LDL-C compared to placebo. CDEC discussed the applicability of LDL-C reduction as a surrogate marker for CV events in patients with HoFH. The clinical experts highlighted that laboratory assessments of lipids are considered widely accepted surrogates for clinically relevant CV outcomes

and are important in guiding treatment decisions in patients with HoFH in Canadian clinical practice. However, CDEC noted that, despite the available evidence for LDL-C reduction, the effect of evinacumab on CV morbidity and mortality remains uncertain in patients with HoFH.

- During the initial and reconsideration meetings, CDEC discussed the arbitrary treatment thresholds for demonstrating a meaningful reduction in LDL-C with evinacumab. The clinical experts suggested that a 20% reduction in LDL-C was also clinically meaningful, although it was highlighted that any reduction in LDL-C can be important in patients with HoFH. For patients able to access pheresis treatments, CDEC noted that distinguishing the specific effect of evinacumab on lipid levels becomes difficult and must rely on expert opinion. During the reconsideration meeting, CDEC considered the thresholds discussed during the initial meeting and based on the lack of available evidence, could not conclude whether any other arbitrary threshold would be acceptable.
- During the initial and reconsideration meetings, CDEC discussed the use of evinacumab in patients who have not had exposure to PCSK9 inhibitors and the consideration by clinical experts that PCSK9 inhibitors should be attempted in these patients, despite the potential lack of activity given the mechanism of action. CDEC noted that in the ELIPSE trial, nearly 76% of patients had exposure to PCSK9 inhibitors, although no patients in the CL-17100 trial had exposure to PCSK9 inhibitors.
- During the reconsideration meeting, CDEC noted that, for patients with HoFH, there is no consistent definition of an adequate trial of other lipid-lowering therapies. The clinical experts noted to CDEC that clinicians in Canada follow the 2023 European Atherosclerotic Society guidelines, which state that up to 8 weeks of treatment with a combination of the maximally tolerated dose (MTD) of a high-intensity statin and ezetimibe is considered an adequate trial.
- During the reconsideration meeting, CDEC noted that, for subsequent renewal after the initial renewal, there is no evidence or guidelines available to define what is considered clinically meaningful improvement in LDL-C, and the committee noted that for the subsequent renewal, a reduction in LDL-C from baseline that is considered clinically beneficial by the treating physician should be considered.
- The clinical experts noted to CDEC that apheresis and plasmapheresis are invasive, negatively impact patients' health-related quality of life (HRQoL), and disrupt patients' families' daily lives. It was also noted that there is a lack of geographic accessibility of apheresis and plasmapheresis, which may result in additional travel burden and create inequities in the level of care patients may receive, based on geographic location across Canada. The clinical experts also suggested that evinacumab may eliminate or reduce the need for plasmapheresis or apheresis.
- The reduction in the frequency and need for apheresis was an outcome identified as important to patients but was not evaluated in the submitted trials. CDEC and the clinical experts highlighted the potential for evinacumab to reduce the frequency of apheresis, which may result in improved HRQoL for patients with HoFH, although there was no evidence to support this.
- CDEC noted that, while statins and ezetimibe are not indicated for pediatric patients with HoFH, these treatments are currently prescribed for these patients in current clinical practice in Canada.

- CDEC discussed ethical and equity considerations related to evinacumab, including those related to the significant physical, emotional, and psychosocial burdens of living with HoFH, such as the burdensome nature of and geographic barriers in access to alternative treatment options like apheresis. As the onset of HoFH typically occurs in childhood, the committee discussed how pediatric patients may be considered particularly vulnerable, given that they are dependent on their parents to provide the necessities of life, and in the context of HoFH, to advocate for and facilitate access to their diagnosis and support for their condition. The committee discussed how, as an IV therapy, evinacumab is not anticipated to present additional (and may involve fewer) geographic barriers to access than those associated with apheresis. However, CDEC noted that telemedicine could be leveraged to potentially facilitate specialist involvement. The committee discussed the high cost of evinacumab; the need to consider distributive justice or the fair allocation of benefits and burdens in the potential implementation of evinacumab for patients for whom alternatives are especially burdensome; and the possible role of prescribing, renewal, and discontinuation criteria in identifying patients most likely to benefit from evinacumab.

Background

Familial hypercholesterolemia (FH) is a genetic disorder characterized by markedly elevated plasma levels of LDL-C from birth that persist throughout life and can lead to the early development of ASCVD. FH can be further subdivided into heterozygous FH (HeFH) and homozygous FH (HoFH) disease, with HoFH being the more severe and rare form of the disease. HoFH is characterized by profoundly elevated plasma levels of LDL-C from birth, putting HoFH patients at a significantly increased risk of early CV events (including myocardial infarction [MI], stroke, and heart failure), and if left untreated, patients with HoFH can be at risk of sudden cardiac death as early as childhood or adolescence.

Diagnosis of HoFH can be made based on clinical criteria or genetic confirmation, although historically, HoFH has been more commonly diagnosed based on clinical presentation, due to the lack of widespread availability of genetic testing in Canada. The Canadian Cardiovascular Society (CCS) Position Statement on FH lacks specific guidance for diagnostic differentiation between HeFH and HoFH; however, clinicians in Canada use the clinical diagnostic features of HoFH per the recently updated 2023 European Atherosclerosis Society (EAS) guidelines, which include untreated LDL-C levels greater than 10.0 mmol/L (400 mg/dL), or LDL-C greater than or equal to 8 mmol/L (300 mg/dL) while on conventional lipid-lowering therapies (LLTs). Additional clinical features include the presence of xanthomas before the age of 10 years, or the presence of HeFH in both parents. Genetic confirmation of diagnosis is based on the identification of biallelic pathogenic variants at the low-density lipoprotein receptor (LDLR), apolipoprotein B (Apo B), PCSK9, or low-density lipoprotein receptor adaptor protein 1 (LDLRAP1), or at least 2 such variants at different loci.

There are an estimated 145,000 patients with FH in Canada, although recent studies in unselected general populations suggest that HoFH may affect as many as 1 in 300,000 people, and may be higher in populations with a founder effect such as one that has been observed in French Canadians, with an estimated prevalence of 1 in 250,000. Overall, there are approximately 80 known cases of HoFH in Canada, and in 2022, there were

52 patients with confirmed HoFH enrolled in the Canadian HoFH Registry, with a majority (69%) found in Quebec, attributable predominantly to founder effects. Patients with HoFH are at a 100-fold elevated risk for MI compared to those without the condition. Untreated patients with HoFH who are LDLR-negative (i.e., who have a complete loss of LDL function) rarely survive beyond the second decade of life, while patients who are LDLR-defective (i.e., who have partial LDLR activity) have a better prognosis, although most develop clinically significant ASCVD by the age of 30 years if left untreated.

The overarching goal of therapy for HoFH is to lower LDL-C and, subsequently, the risk of ASCVD. The lowering of plasma cholesterol levels is known to reduce CV events, coronary heart disease mortality, and all-cause mortality. Recommended lifestyle modifications, as per the CCS guidelines on the diagnosis and treatment of dyslipidemias, include weight control, reducing the amount of fat intake to less than 30% of daily calories, consuming 10 g to 20 g of fibre per day, and increased physical activity. Additional lifestyle changes include smoking cessation and limiting alcohol intake. Statins are the primary pharmacological intervention to achieve control of LDL-C in patients with hypercholesterolemia. Most patients with hypercholesterolemia should be initiated on the MTD of high-intensity statins (atorvastatin or rosuvastatin), with the goal of lowering LDL-C by at least 50%. In cases of primary prevention, where the LDL goal is unmet through statin therapy alone, add-on ezetimibe or bile acid sequestrants (or both) is recommended, further reducing LDL-C by 10% to 40% (average 20%). If LDL goals are still not met, PCSK9 inhibitors (evolocumab) are available to patients meeting certain criteria as an adjunct treatment to diet, MTD statins and ezetimibe. However, given that traditional LLTs such as statins and PCSK9 inhibitors act by upregulating LDLR expression, they have little efficacy in HoFH patients and virtually no activity in those with 2 null LDLR alleles. Nearly all patients with HoFH will require extracorporeal LDL-C removal, particularly if the LDL-C levels remain greater than 5 mmol/L despite treatment, or if ASCVD is present. Either plasmapheresis or preferably LDL-C apheresis should be started as soon as technically feasible, usually before the age of 5 years and at least by the age of 8 years.

Evinacumab (Evkeeza) is a recombinant human monoclonal antibody that binds to and inhibits angiopoietin-like 3 (ANGPTL3), a member of the angiopoietin-like protein family that is expressed primarily in the liver and plays a role in the regulation of lipid metabolism by inhibiting lipoprotein lipase (LPL) and endothelial lipase (EL). Inhibition of ANGPTL3 via evinacumab lowers triglycerides and high-density lipoprotein cholesterol (HDL-C) by releasing LPL and EL. Evinacumab reduces LDL-C independent of LDLR by promoting very low-density lipoprotein (VLDL) processing and VLDL remnants clearance upstream of LDL formation through an EL-dependent mechanism.

Evinacumab has been approved by Health Canada as an adjunct to diet and other LDL-C–lowering therapies for the treatment of adult and pediatric patients aged 5 years and older with HoFH. Evinacumab is a recombinant human monoclonal antibody, which specifically binds to and inhibits ANGPTL3. It is available as a 150 mg/mL concentrate for solution for infusion, and the dosage recommended in the product monograph is 15 mg/kg administered by IV infusion over 60 minutes every 4 weeks.

Sources of Information Used by the Committee

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

- a review of 2 clinical studies: 1 phase III RCT, and 1 single-arm, open-label study in patients with HoFH
- patient perspectives gathered by patient groups, the Canadian Heart Patient Alliance (CHPA) and the Canadian Organization for Rare Disorders (CORD)
- input from public drug plans and cancer agencies that participate in the CADTH review process
- input from 2 clinical specialists with expertise diagnosing and treating patients with HoFH
- input from 1 clinician group, Familial Hypercholesterolemia Canada (FH Canada)
- a review of the pharmacoeconomic model and report submitted by the sponsor
- a review of relevant ethical issues related to evinacumab from published literature.

Stakeholder Perspectives

Patient Input

CADTH reviewed 1 joint patient input from CHPA and CORD. Information from respondents was gathered via an online survey that ran from April 12, 2023, to May 7, 2023, as well as individual interviews conducted with patients with HoFH and caregivers. All patients (N = 18) resided in Canada, mostly in Ontario (12 [66.7%]), with 3 (16.7%) each in British Columbia and Quebec. Regarding the impact of HoFH on patients, about 75% of respondents had experienced severe (very high) levels of LDL-C and 25% reported moderate levels of LDL-C. Around 50% of the respondents reported that they had experienced moderate or severe CV events, including atherosclerosis, stroke, atrial fibrillation, and/or cardiac infarction, and half of the patients had experienced severe chest pains or had xanthomas. Patients and caregivers highlighted that living with HoFH was associated with stress due to physical symptoms and the uncertainty or unpredictability of the future, with younger patients noting that HoFH impacted their education and social life, partly because of the time required for treatment. Patients expressed the need for treatment options that can reliably, consistently, and sustainably control LDL-C levels at normal or near-normal levels, allowing them to experience fewer spikes, reducing the frequency and need for apheresis, and reducing the risk of CV events. Patients with HoFH questioned the effectiveness of current treatment options (apheresis, statins, and other medications) in managing their LDL-C levels, highlighting the concerns of undergoing surgery in advance of or because of future CV events, further impacting their HRQoL and life expectancy. Of the 18 patients who provided input, 6 reported having access to or experience with evinacumab through a clinical trial, compassionate access program, or research study. Patients indicated that they were satisfied with evinacumab, as the treatment consistently lowered their LDL-C levels and improved their HRQoL through reduced frequency of apheresis, improvements in energy, and the ability to participate in social and family events and attend school. Additionally, there were no reports of serious adverse events (SAEs) following the use of evinacumab.

Clinician Input

Input From Clinical Experts Consulted by CADTH

The information in this section is based on input received from a panel of 4 clinical specialists consulted by CADTH for the purpose of this review.

HoFH is a rare disease, and patients with HoFH are diagnosed based on standard, well-established clinical and genetic criteria, although genetic confirmation is not required. Patients present at an early age with extremely elevated LDL-C levels (untreated LDL-C greater than or equal to 10 mmol/L), as well as other clinical characteristics including the presence of xanthomas. The clinical experts noted that there are currently multiple established guidelines for the management of dyslipidemia, and highlighted the recent publication of the EAS Consensus Statement of HoFH. The experts noted that current guideline-recommended LDL-C thresholds are pragmatic and remain well above the acceptable level for patients without hypercholesterolemia. Per the current guidelines, the target LDL-C level for patients with HoFH is below 2.5 mmol/L; however, the experts agreed that this value is pragmatic and arbitrary, based on other treatments and clinical trial criteria.

The clinical experts highlighted that survival for HoFH patients has nearly doubled in a generation due to the LLTs available; however, they noted that repeated CV events — including MI, aortic valve stenosis, and aortic root disease — and the need for revascularization have increased. As such, the clinical experts emphasized that the main goal of treatment for patients with HoFH is to reduce LDL-C aggressively and safely over the longest term possible to prevent premature CV disease (CVD). In the pediatric population, the goal of LDL-C–lowering treatment is to prevent or delay ASCVD and obviate the need for or reduce apheresis. For adults, the goal of LDL-C–lowering treatment is to slow or halt ASCVD and potentially reverse it and its progression to clinically manifest CVD.

Most currently available pharmacological treatments only target the function of LDLR, rendering them less effective in HoFH, and they are more effective in patients with residual LDLR function, rather than “null” mutations where there is no functional LDLR. The clinical experts noted that once a patient is diagnosed, they are immediately put on the MTD of statins and ezetimibe therapy. In most cases, this combination is insufficient to meet the desired LDL-C targets. To further reduce LDL-C levels, PCSK9 inhibitors may be tried; however, the experts noted that, given the pathophysiology of HoFH and the mechanism of action of PCSK9 inhibitors, response may be limited although it should still be attempted. Often statins, ezetimibe, and PCSK9 inhibitors do not achieve sustained and significant reductions of LDL-C to levels below 2.5 mmol/L and/or a 50% lowering of LDL-C. If LDL-C levels are still above the goal, other treatment options — including lomitapide with or without extracorporeal removal of circulating LDL-C — may be attempted; however, these other treatment options have a notable impact on HRQoL as lomitapide is associated with the need for severe dietary restrictions, as well as adverse reactions and poor tolerability or compliance. In addition, extracorporeal removal of LDL-C, while effective, is extremely invasive, burdensome, and associated with a rebound period during which LDL-C levels rise to baseline, requiring recurrent and sustained treatment cycles. The experts highlighted the need for a drug that is safe and effective to lower baseline levels to a similar degree to that achieved with pheresis, without the same burden. The experts also noted that not

all patients are able to access the full armamentarium of treatments available, and access to pheresis may be limited in Canada, with only 4 centres in Canada (Toronto, London, Québec City, and Edmonton). Plasmapheresis, which is more widely available, is considered a less optimal substitute for LDL apheresis.

The experts highlighted that evinacumab would likely be used as an add-on to MTD statins, ezetimibe, and/or PCSK9 inhibitors, preferentially with the hope of supplanting lomitapide and either delaying or reducing the frequency of pheresis.

The experts highlighted that the selection of patients most in need of intervention with evinacumab is not entirely based on disease characteristics but would be preferred in patients with an LDL greater than 2.5 mmol/L despite maximally tolerated therapy, and would be preferentially used in patients receiving or being considered for lomitapide or those on or being considered for apheresis, based on the poor risk-benefit profile of lomitapide and the burden of extracorporeal LDL-C removal. Per the clinical experts, patients most likely to benefit from treatment with evinacumab are those diagnosed with HoFH who have experienced limited or inadequate response to available LLTs. In addition to the treatments available, patients with ASCVD, aortic valve disease, or genetic documentation of 2 pathogenic variants represent subsets of high-risk patients for whom evinacumab might be considered. Regarding patients least suitable for treatment, the experts noted that there are no patients with HoFH that they would not consider for evinacumab, and regarding treatment history noted that it is highly unlikely that patients would be able to meet desirable LDL-C targets on conventional statin and ezetimibe therapy alone.

The clinical experts agreed that the most important outcome of treatment is the reduction of CV morbidity or mortality; however, they noted that LDL-C is the most reasonable surrogate outcome used by clinicians to avoid all downstream ASCVD complications. Additionally, the clinical experts noted that current clinical trials aim to address important outcomes that are used in clinical practice, and measuring event-driven outcomes is unreasonable in this population due to the rarity of the disease and the length of time before events accrue. Additionally, from a functional perspective, avoidance of pheresis options would be a measure of treatment success, although there are currently no data to demonstrate this potential benefit yet. Additionally, while the experts noted there are no data, they mentioned that patients' disease should be stable on evinacumab for 6 months before attempting to reduce the frequency of or remove pheresis.

When deciding to discontinue treatment, the clinical experts agreed that treatment would be discontinued in patients who experience severe adverse events (AEs) including anaphylactic or infusion reactions that are unable to be managed. Additionally, the experts agreed that any new AEs that were identified could be cause for discontinuation, given the small sample size included in the trials for evinacumab. The experts noted that progression of atherosclerosis, major adverse cardiac events (MACEs), or lack of response to treatment may still occur with sustained treatment; however, the experts stated that this would not prompt discontinuation of treatment. While there is no strict definition for lack of response in this population, the experts highlighted that arbitrary LDL-C cut points would be chosen for determining an acceptable LDL-C reduction, although this would be contextual for each individual patient. However, the experts also emphasized that it would be inappropriate to discontinue or deny access to therapies that provide any safe lowering of LDL-C. For example, the experts noted that a treatment offering patients a 20% reduction in LDL-C might be below an

arbitrary 30% cut-off, however, the experts agreed that they would not likely discontinue treatment and would not consider a 20% reduction in LDL-C a lack of efficacy.

Patients with HoFH are under the care of specialists with special qualifications in dyslipidemia (e.g., endocrinologists, cardiologists, and lipidologists), and treatment would occur within the specialist's facilities or those accessible to the patient. Patients with HoFH are under the care of a lipid specialist, and are seen as often as every 3 months, and at minimum every 6 months. During pheresis therapy, lipid profiles are conducted before and after pheresis treatment; as such, LDL-C is routinely tracked. The experts noted that as an IV infusion, treatment necessitates an infusion-specific setting, as infusion reactions and flu-like reactions may occur. For patients receiving pheresis treatments, evinacumab would be easiest to administer where extracorporeal machines are located. The experts also noted that vascular access in children may pose a potential challenge. Given the dispersion of the population, the experts noted that comanagement with primary care physicians could be envisioned, and administration of evinacumab outside the specialist setting may be possible under the remote supervision of a specialist. The experts also highlighted that experience with evinacumab is limited; therefore, moving treatment into the community setting may be possible in the future although not likely to occur yet.

Clinician Group Input

One clinician group, FH Canada, provided input for this review. Information from this group was gathered through the collective clinical experience of 7 clinical experts, published literature, and congress proceedings. Overall, the clinician group noted that there is an unmet need for equitably accessible therapies that safely and effectively treat HoFH patients. The clinician group highlighted that the current treatment options (statins, ezetimibe, and PCSK9 inhibitors, with or without plasmapheresis or apheresis), are inadequate in lowering LDL-C in patients with HoFH due to lack of efficacy and differences in mechanism of action (with statins, ezetimibe, and PCSK9 inhibitors), lack of tolerability (with lomitapide), and invasiveness (i.e., reduced HRQoL and disruption to patients' and families' daily lives [with apheresis and plasmapheresis]). Additionally, the clinician group highlighted the lack of availability of apheresis and plasmapheresis given that it is limited to major academic centres, resulting in additional travel burden, and creating inequities in the level of care of patients based on geographic location across Canada. Patients best suited for treatment with evinacumab, according to the clinician group, are those whose LDL-C levels do not meet the target levels with current treatments, or those with progressive CVD despite the use of current treatments. The clinician group indicated that evinacumab would likely be used as a fourth-line therapy after statins, ezetimibe, and PCSK9 inhibitors, and suggested that evinacumab may eliminate or reduce the need for plasmapheresis or apheresis and possibly lomitapide. In line with the clinical experts consulted by CADTH, the clinicians from FH Canada considered reduction in LDL-C levels to be the most important outcome of treatment. The clinician group cited a sustained reduction in LDL-C greater than 20% to 30% as a meaningful response to treatment. An additional important outcome for assessing response to treatment included reduction in the frequency of apheresis or plasmapheresis. The clinician group noted that intolerable side effects would be the primary factor when deciding to discontinue treatment.

Drug Program Input

Input was obtained from the drug programs that participate in the CADTH reimbursement review process. The clinical experts consulted by CADTH provided advice on the potential implementation issues raised by the drug programs.

Table 2: Responses to Questions From the Drug Programs

Implementation issues	Response
Relevant comparators	
In the ELIPSE trial, 93.8% of patients were on statins, 75.4% were on ezetimibe, and 76.9% were on a PCSK9 inhibitor. For other treatments, 21.5% of patients were receiving lomitapide at baseline, and 33.8% were on lipoprotein apheresis. Lomitapide was given a Do Not List recommendation by CADTH in 2015 and is only publicly funded in Quebec. Few centres in Canada have the infrastructure for lipoprotein apheresis. A large proportion of patients in the pivotal trial are receiving therapy with treatments that have limited access in Canada. Are these proportions reflective of the population in Canada? How accessible is lipoprotein apheresis in Canada? Is it expected that patients would be using these treatments, or would have to have tried them before they receive evinacumab?	The clinical experts cited a recent study using data from the FH Canada registry to compare the lipid-lowering therapies used in the ELIPSE trial with patients in Canada within the registry. Differences were noted in the proportion of patients receiving PCSK9 inhibitors between the ELIPSE trial and the FH Canada registry, which they noted to be likely reflective of the trial population and a result of PCSK9 access issues in Canada. The experts emphasized that PCSK9 inhibitors should be tried in patients with HoFH as some patients do respond to treatment despite the known mechanism of action focusing on LDLR activity, which has minimal to no activity in HoFH. Additionally, the experts noted that the proportion of patients receiving apheresis was higher in the FH registry than in the ELIPSE trial. The experts emphasized that only 4 centres in Canada (Toronto, London, Québec City, and Edmonton) can conduct LDL apheresis. However, the FH Canada registry population also included plasmapheresis, which the experts noted is more readily available across Canada than LDL apheresis, although issues may arise when attempting to access other extracorporeal removal services, as these facilities are currently overwhelmed with patients for other diseases. The procedure is also considered a poor surrogate for LDL apheresis. Contextually, the experts considered the treatment distribution of the ELIPSE trial to be relatively generalizable to the Canadian population, although the order of treatment sequencing with lomitapide, pheresis, and evinacumab is likely to shift should evinacumab become available.
The proposed indication for evinacumab is for pediatric and adult patients aged 5 years or older. There is limited access to many relevant comparators in Canada, which may be further restricted from the pediatric population by current funding criteria (e.g., PCSK9 inhibitors). Is access expected to be further limited for younger patients?	Most drugs in the pediatric HoFH population are used off-label. The experts noted that, in their experience, accessing PCSK9 inhibitors for children poses many administrative challenges. They further noted that, for most therapies, age cut-offs are inappropriate as most patients with HoFH are diagnosed before the age of 4 years. The experts also highlighted that starting extracorporeal removal of LDL in patients younger than 5 years can be challenging due to equipment constraints as well as the concern of maintaining long-term vascular access. The experts hypothesized that evinacumab may be of great importance in the younger population due to the potential for delaying the requirement for apheresis to a time when it may be less burdensome or challenging.
Considerations for initiation of therapy	
Based on the proposed indication, how many lipid-lowering therapies would have to be tried before initiating treatment with evinacumab?	At diagnosis, patients with HoFH are placed on MTD statins, ezetimibe, and PCSK9 inhibitors, if available. CDEC and the clinical experts noted that access to PCSK9 inhibitors is limited in Canada, although the

Implementation issues	Response
	experts noted that they should still be attempted. Further, in Quebec, patients may receive lomitapide, although there are certain dietary restrictions and monitoring requirements, including monitoring for fatty liver. Patients may also be placed on apheresis to remove circulating LDL-C. The experts stated that evinacumab would likely be used following MTD statins, ezetimibe, and PCSK9 inhibitors, and may reduce the need for or frequency of apheresis.
Considerations for continuation or renewal of therapy	
Are the thresholds for demonstrating a meaningful reduction in LDL-C in patients with HoFH the same as those used for PCSK9 inhibitors in patients with HeFH?	The clinical experts noted to CDEC that the thresholds for a meaningful reduction in LDL-C in patients with HoFH are different than those used for PCSK9 inhibitors in patients with HeFH. In addition, the clinical experts noted that there is no strict definition for lack of response in patients with HoFH. They also highlighted that arbitrary LDL-C cut points would be chosen for determining an acceptable LDL-C reduction, although this would be contextual for each individual patient. The clinical experts also emphasized that it would be inappropriate to discontinue or deny access to therapies that provide any safe lowering of LDL-C.
Considerations for prescribing of therapy	
Evinacumab is administered q.4.w. via 60-minute IV infusion. The administration setting may vary by jurisdiction and may limit where coverage would be provided.	No response required. For CDEC consideration.
Generalizability	
There was a limited number of patients in each age category in the pivotal ELIPSE trial and in the supporting CL-17100 trial. In the ELIPSE trial, 2 patients were aged between 12 and 17 years, 39 patients were aged between 18 and 44 years, 16 patients were aged between 45 and 64 years, and 8 patients were aged 65 years or older. In the CL-17100 trial, 11 patients were aged between 5 and 9 years, and 9 patients were aged between 10 and 12 years. Given the limited number of patients in each age category, can the results for each age group be considered generalizable to the overall HoFH population?	CDEC and the clinical experts noted that conducting a controlled trial in pediatric and adult patients with HoFH is difficult due to the rarity of the disease. The clinical experts considered the results of the pivotal studies to be generalizable despite the ages of enrolled patients, and noted that the mechanism of action of evinacumab is not likely impacted by the age of patients. Furthermore, the experts considered their own experience with evinacumab in patients younger than 18 years and did not express concern with the generalizability of the results based on age.
The primary end point of the pivotal trial was LDL-C reduction. What evidence is there for reduction in CV events or improved mortality?	Event-driven outcomes are difficult to observe and achieve in this rare and chronic disease. Moreover, patients with HoFH are heterogenous in their response due to confounding effects of concomitant therapy, which can vary. Overall, it was noted that there is no trial or epidemiological evidence yet for the reduction in CV events or improved mortality with evinacumab; however, the experts consider LDL-C to be the most appropriate surrogate outcome in patients with HoFH, as sustained and safe LDL-C lowering has consistently been associated in the long term with event reductions using other drugs.

Implementation issues	Response
	The experts also emphasized that, over the past generation, survival in patients with HoFH has nearly doubled, which they stated was attributable to lipid-lowering therapies.
Care provision issues	
Evinacumab is administered q.4.w. via 60-minute IV infusion. In what setting would evinacumab be administered in most provinces? Would this differ by age? Would you expect any challenges in administering this treatment?	Treatment with evinacumab would be administered within a hospital or infusion clinic under the care of a specialist with experience treating patients with HoFH. Vascular access in children tends to pose some challenges; therefore, expertise available in hospitals may be required. Adverse reactions with evinacumab were limited in the trials; however, given the small sample size, there is the potential for new, unknown adverse reactions. Consideration should also be given to community clinics that have the expertise to administer IV drugs. Although there is no experience with evinacumab, remote comanagement with lipid specialists in the community may be possible. In general, for patients also undergoing pheresis, evinacumab would be administered following the pheresis treatment; with appropriate dosage timing, it would not impact the pharmacokinetics of evinacumab.

CDEC = CADTH Canadian Drug Expert Committee; CV = cardiovascular; FH = familial hypercholesterolemia; HeFH = heterozygous familial hypercholesterolemia; HoFH = homozygous familial hypercholesterolemia; LDL = low-density lipoprotein; LDL-C = low-density lipoprotein cholesterol; LDLR = low-density lipoprotein receptor; MTD = maximally tolerated dose; PCSK9 = proprotein convertase subtilisin/kexin type 9; q.4.w. = every 4 weeks.

Clinical Evidence

Systematic Review

Description of Studies

Two studies — the CL-1629 (ELIPSE) trial and CL-17100 trial — were included in this review. The ELIPSE trial was a pivotal, phase III, double-blind, randomized placebo-controlled trial designed to evaluate the efficacy and safety of evinacumab versus placebo in pediatric and adult patients with HoFH. A total of 65 patients were randomized 2:1 to evinacumab 15 mg/kg every 4 weeks or matching placebo. Three patients were enrolled from Canadian investigative sites. The primary outcome of the ELIPSE trial was the change from baseline in LDL-C at week 24. Secondary outcomes included the percent change from baseline to week 24 in Apo B, non-HDL-C, and total cholesterol; the proportion of patients with greater than or equal to 30% and greater than or equal to 50% reduction in LDL-C at week 24; the absolute change in LDL-C from baseline to week 24; the proportion of patients with LDL-C less than 100 mg/dL (2.59 mmol/L) at week 24; and the proportion of patients who meet EU or US apheresis eligibility criteria at week 24.

The CL-17100 study, which was considered a supportive trial for this review, included 3 parts (parts A, B, and C). Part A was a phase Ib, single-arm, single-dose, pharmacokinetic and pharmacodynamic study consisting of a 16-week, open-label treatment period; it enrolled 6 patients with HoFH. Only parts B and C were of interest to this review. Part B was a 24-week, phase III, single-arm, open-label study to assess the

efficacy and safety of evinacumab in pediatric patients aged 5 to 11 years with HoFH. A total of 14 patients were enrolled into part B, and no patients from part A were enrolled into part B. Upon completion of part B, all patients continued into Part C. Part C is an ongoing extension period consisting of the 20 patients who completed part A (N = 6) and part B (N = 14). Part C consisted of a 48-week treatment period and a 24-week follow-up period after the last dose of evinacumab. The final dose in part C was the same as the dose in part B (15 mg/kg IV every 4 weeks). The data cut-offs for parts B and C were January 31, 2022, and [redacted], respectively. The primary outcomes of parts B and C were identical to the ELIPSE trial, with secondary outcomes of percent change from baseline to week 24 in Apo B, non-HDL-C, and total cholesterol; the proportion of patients with greater than or equal to 50% reduction in LDL-C at week 24; the absolute change in LDL-C from baseline to week 24; and the proportion of patients with LDL-C less than 100 mg/dL (2.59 mmol/L) at week 24.

In the ELIPSE trial, there was a difference between evinacumab and placebo groups in terms of age at baseline, with a mean age of 44.3 years (standard deviation [SD] = 16.8) in the evinacumab group compared to 36.7 years (SD = 11.52) in the placebo group. Only 1 patient in each treatment group was younger than 18 years. In line with the difference in age, there was also a difference in mean time from diagnosis of HoFH, with the mean time from diagnosis of 16.15 years (SD = 14.562) in the evinacumab group compared to 10.65 years (SD = 12.537) in the placebo group. A total of 48.8% of patients had homozygous LDLR mutations in the evinacumab group compared to 31.8% in the placebo group, while fewer patients in the evinacumab group had compound heterozygous mutations compared to those in the placebo group (27.9% versus 36.4%). Most patients had received at least 3 LLTs (69.8% versus 50.0%), consisting mostly of the combination of statins plus ezetimibe and a PCSK9 inhibitor (48.8% versus 36.4%). More patients in the evinacumab group had received lomitapide than in the placebo group (25.6% versus 13.6%). Lipid parameters were comparable across treatment groups (LDL-C, 259.5 mg/dL versus 246.5 mg/dL; Apo B, 169.1 mg/dL versus 175.9 mg/dL; non-HDL-C, 281.9 mg/dL versus 269.9 mg/dL; and total cholesterol, 325.6 mg/dL versus 315.9 mg/dL).

The CL-17100 study was conducted in pediatric patients with HoFH aged 5 to 11 years. The mean age of patients enrolled in part B of the CL-17100 study was 9.1 years (SD = 1.94). Most patients (71.4%) had compound heterozygous mutations, and 50% of patients had had prior apheresis at baseline. Nearly all patients had been treated with statins (85.7%) and ezetimibe (92.9%), and only 2 patients (14.3%) had received lomitapide. Lipid parameters at baseline were similar to the ELIPSE trial, with LDL-C of 263.7 mg/dL, Apo B of 168.2 mg/dL, non-HDL-C of 282.2 mg/dL, and total cholesterol of 315.5 mg/dL.

Efficacy Results

Percent Change From Baseline in LDL-C

During the 24-week double-blind period of the ELIPSE trial, the least squares mean (LSM) percent change from baseline with evinacumab was −47.1% (standard error [SE] = 4.6), compared to 1.9% (SE = 6.5) with placebo. In the double-blind treatment period, the LSMD between evinacumab and placebo in percent change in LDL-C from baseline at 24 weeks was −49.0% (95% confidence interval [CI], −65.0 to −33.1), favouring evinacumab. During the open-label treatment period of ELIPSE, the overall percent reduction in LDL-C at 48

weeks in the open-label treatment period was −46.31% [redacted]. Results of sensitivity analyses and subgroup analyses by background LLT, apheresis status, baseline LDL-C level, and HoFH genotype were consistent with the primary analysis, in favour of evinacumab.

In the CL-17100 study, results for LSM change from baseline in LDL-C with evinacumab from part B and the pooled part B and C were consistent with the double-blind period of the ELIPSE trial, with percent reductions of −48.32% [redacted] at 24 weeks, respectively.

Absolute Change From Baseline in LDL-C

The absolute change from baseline in LDL-C during the 24-week double-blind treatment period of ELIPSE was −134.7 mg/dL (SE = 12.4) in the evinacumab group compared to −2.6 mg/dL (SE = 17.6) in the placebo group, favouring evinacumab (LSMD = −132.1 mg/dL [95% CI, −175.3 to −88.9]; P < 0.0001). In the open-label treatment period, [redacted].

In part B of the CL-17100 study, the LS mean absolute change from baseline in LDL-C was −131.9 mg/dL (SD, 30.0).

Proportion of Patients With Greater Than or Equal to 30% Reduction in LDL-C

In the 24-week double-blind treatment period of the ELIPSE trial, 83.7% of patients in the evinacumab group and 18.2% of patients in the placebo group experienced a greater than or equal to 30% reduction in LDL-C, favouring evinacumab (odds ratio [OR] = 25.2 [95% CI, 5.7 to 110.5]; P < 0.0001).

The proportion of patients with a greater than or equal to 30% reduction in calculated LDL-C at week 24 was not evaluated in the open-label treatment period of the ELIPSE trial or in the CL-17100 study.

Percent Change From Baseline in Apo B

In the ELIPSE trial, during the 24-week double-blind treatment period, the LSM percent change from baseline in Apo B was −41.4% (SE = 3.3) with evinacumab compared to −4.5% (SE = 4.8) with placebo, favouring evinacumab (LSMD = −36.9% [95% CI, −48.6 to −25.2]). The overall percent reduction in LDL-C at 48 weeks in the open-label treatment period was [redacted].

In the CL-17100 study, the LSM change from baseline in Apo B with evinacumab from part B [redacted] was −41.32% [redacted]

Proportion of Patients With LDL-C Less Than 100 mg/dL (2.59 mmol/L)

The proportion of patients with LDL-C less than 100 mg/dL (2.59 mmol/L) at 24 weeks was 46.5% in the evinacumab group compared to 22.7% in the placebo group (OR = 5.7 [95% CI, 1.3 to 24.9]; P = 0.0203).

The proportion of patients with LDL-C less than 100 mg/dL was not evaluated in the open-label treatment period of the ELIPSE trial or in the CL-17100 study.

Proportion of Patients With LDL-C Less Than 70 mg/dL (1.81 mmol/L)

In the ELIPSE trial, the proportion of patients with LDL-C less than 70 mg/dL (1.81 mmol/L) at 24 weeks was 27.9% in the evinacumab group compared to 4.5% in the placebo group (OR = 20.9 [95% CI, 1.6 to 276.8]; P = 0.0209).

The proportion of patients with LDL-C less than 70 mg/dL was not evaluated in the open-label treatment period of the ELIPSE trial or in the CL-17100 study.

Proportion of Patients Who Met US Apheresis Criteria

In the ELIPSE trial, the proportion of patients who met US apheresis eligibility criteria at 24 weeks was 7.0% in the evinacumab group compared to 22.7% in the placebo group (OR = 0.1 [95% CI, 0.0 to 1.3]; P = 0.0845). Statistical hypothesis testing was terminated at this end point in the ELIPSE trial because statistical significance was not reached.

The proportion of patients who met US apheresis eligibility criteria was not evaluated in the open-label treatment period of the ELIPSE trial or in the CL-17100 study.

Proportion of Patients Who Met EU Apheresis Criteria

In the ELIPSE trial, the proportion of patients who met EU apheresis eligibility criteria at 24 weeks was 32.6% in the evinacumab group compared to 77.3% in the placebo group (OR = 0.1 [95% CI, 0.0 to 0.3]).

The proportion of patients who met EU apheresis eligibility criteria was not evaluated in the open-label treatment period of the ELIPSE trial or in the CL-17100 study.

EQ-5D Score

In the ELIPSE trial, the mean EQ-5D utility score at 24 weeks was [redacted] for evinacumab and [redacted] for placebo, representing a mean change from baseline of [redacted] with evinacumab, and [redacted] with placebo.

Quality of life was not evaluated in the open-label treatment period of the ELIPSE trial or in the CL-17100 study.

Mortality (All-Cause and CV-Related)

All-cause and CV-related mortality were not evaluated in the ELIPSE or CL-17100 studies.

CV-Related Morbidity

CV-related morbidity outcomes, such as the incidence of resuscitated cardiac arrest, nonfatal MI, and stroke, were not evaluated in the ELIPSE or CL-17100 studies.

Harms Results

In the ELIPSE trial, the incidence of treatment-emergent adverse events (TEAEs) was lower for patients treated with evinacumab compared to placebo during the double-blind treatment period (65.9% versus 81.0%). In the open-label treatment period of the ELIPSE trial, the incidence of TEAEs for evinacumab [redacted]. The most common TEAEs in patients treated with evinacumab versus placebo included nasopharyngitis (15.9% versus 23.8%) and influenza-like illness (11.4% versus 0.0%). In the open-label treatment period, the most frequently reported TEAEs [redacted]. SAEs in the ELIPSE trial occurred in 2 (4.5%) patients in the evinacumab group and consisted of urosepsis (1 [redacted]) and attempted suicide (1 [redacted]). There were no SAEs in the placebo group. There were no withdrawals due to AEs or deaths reported during the ELIPSE study. In terms of notable harms, 4 patients (9.1%) in the evinacumab

group and 3 patients (14.3%) in the placebo group experienced allergic events, and 3 patients in the evinacumab group (6.8%) and 1 patient in the placebo group (4.8%) experienced infusion-related reactions (IRRs) during the double-blind treatment period of ELIPSE.

In the CL-17100 study, [redacted] One patient (5.0%) experienced an SAE of tonsillitis. There were no withdrawals due to AEs or deaths reported during the CL-17100 study. [redacted].

Critical Appraisal

The ELIPSE trial was a first-in-class, phase III, placebo-controlled RCT that included both double-blind and open-label treatment periods. Appropriate methods for randomization (using interactive response technology), treatment allocation (stratified by apheresis treatment and by region), and maintenance of blinding to treatment assignment were used, reducing selection, performance, and detection biases. The CL-17100 study was an open-label, single-arm study of evinacumab in patients with HoFH aged 5 to 11 years. The choice to conduct a single-arm trial in the younger population was justified considering the rarity of the indication and the age of the participants; however, the noncomparative nature negates the ability to draw definitive conclusions on the effectiveness of evinacumab due to the small sample size and chronic progression of HoFH. As such, the strength and interpretability of the results for this group of patients is limited. Dropouts and missing data in the ELIPSE and CL-17100 studies were low. The primary end point of the ELIPSE trial used a mixed-effect model with repeated measures to account for missing data under the missing at random assumption, which may not hold in this setting and lead to overconfidence in the effect size. The sensitivity analyses used a pattern mixture model to account for nonignorable missingness, although overall, missing data were low and unlikely to impact the results. Acceptable methods to account for multiplicity were used in the ELIPSE trial. The primary and key secondary end points were controlled for multiplicity at the 0.05 level using a hierarchical testing sequence. However, at the end point of proportion of patients who met US apheresis eligibility criteria, statistical significance was not achieved; thus, the multiple testing procedure failed, and all subsequent outcomes (the proportion of patients with LDL-C less than 100 mg/dL, and the proportion of patients who meet EU apheresis eligibility criteria) should only be viewed as supportive. While they generally supported the primary analysis, subgroup analyses in the ELIPSE and CL-17100 trials were not statistically powered to detect within-group or between-group differences; therefore, the results from the subgroup analyses should be interpreted as supportive evidence only for the overall effect of evinacumab.

The clinical experts consulted by CADTH indicated that the inclusion and exclusion criteria for the ELIPSE and CL-17100 studies were appropriate, although they highlighted that genetic confirmation of HoFH is not always conducted. Both the ELIPSE and CL-17100 studies were multinational studies; however, the ELIPSE trial was the only study to enrol patients in Canada (N = 3), although given the low number of patients in Canada enrolled, generalizability based on geography cannot be assumed. HoFH is a rare disease, which expectedly resulted in the small sample sizes for the ELIPSE and CL-17100 studies. In total, the ELIPSE trial included 65 patients with HoFH, and the CL-17100 trial included 20 patients. The clinical experts consulted by CADTH noted that, in their experience, the populations included in the trials were generally in

line with clinical practice in Canada with regard to age of patients and LDL-C levels at baseline. The chosen comparator of placebo in the ELIPSE study was appropriate and aligns with the recommended standard of care guidelines for HoFH in Canada, for which the experts noted that standard of care consists of MTD statins, ezetimibe, and a PCSK9 inhibitor. The clinical experts consulted by CADTH noted that the proportion of patients receiving various LLTs was in line with the general patient population with HoFH, although the proportion of patients in the ELIPSE trial receiving PCSK9 inhibitors was higher than in Canadian clinical practice, considering the difficulty accessing PCSK9 inhibitors in Canada. There were minor differences in lomitapide use at baseline, with only 11 patients (25.6%) in the evinacumab group and 3 patients (13.6%) in the placebo group receiving lomitapide, although this was potentially related to the rarity of the disease and study design, as differences in patients may be more noticeable in studies with small sample sizes. The outcomes used to inform the efficacy of evinacumab in the ELIPSE and CL-17100 studies were chosen based on validated laboratory assessments of lipids and are considered widely accepted surrogates for clinically relevant CV outcomes and important in guiding treatment decisions in Canadian clinical practice in patients with HoFH. In addition to the well-established lowering of LDL-C, the most valuable outcomes to patients with HoFH included the reduction in the risk of CV events and reducing the need for apheresis. The included studies were not designed to assess important CV-related outcomes, including reductions in MACE and all-cause and CV-related mortality, although the clinical experts consulted by CADTH noted that measuring event-driven outcomes like these is difficult in HoFH, due to the rarity of the disease. Additionally, impact on HRQoL was an exploratory outcome of the ELIPSE trial and was not evaluated in the CL-17100 study. The clinical experts consulted by CADTH noted that reduction in the burden of apheresis requirements is believed to impact patients' HRQoL; however, the measurement of this in the available evidence was not captured. The clinical experts consulted by CADTH emphasized that the duration of the ELIPSE and CL-17100 studies (24 weeks) was considered appropriate for assessing lipid-related outcomes given that the effects on lipids are rapidly seen; however, they noted that the 24-week duration of the included studies was insufficient to determine the impact of evinacumab on CV-related morbidity and mortality, and HRQoL.

Grading of Recommendations Assessment, Development and Evaluation Summary of Findings and Certainty of the Evidence

Methods for Assessing the Certainty of the Evidence

For pivotal studies and RCTs identified in the sponsor's systematic review, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to assess the certainty of the evidence for outcomes considered most relevant to inform CADTH's expert committee deliberations, and a final certainty rating was determined as outlined by the GRADE Working Group. Following the GRADE approach, evidence from RCTs started as high-certainty evidence and could be rated down for concerns related to study limitations (which refer to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias.

The selection of outcomes for GRADE assessment was based on the sponsor's Summary of Clinical Evidence, consultation with clinical experts, and input received from patient and clinician groups and public drug plans. The following list of outcomes was finalized in consultation with expert committee members: reduction in LDL-C levels (percent change from baseline in LDL-C at 24 weeks, absolute change in LDL-C at

24 weeks, proportion of patients with ≥ 30% reduction in LDL-C at 24 weeks, proportion of patients who meet US apheresis eligibility criteria at 24 weeks, proportion of patients with LDL-C < 100 mg/dL [2.59 mmol/L] at 24 weeks, proportion of patients who meet EU apheresis eligibility criteria at 24 weeks, proportion of patients with LDL-C < 70 mg/dL [1.81 mmol/L] at 24 weeks), reduction in other lipid parameters (percent change in Apo B from baseline at 24 weeks), and improved HRQoL (change from baseline in EQ-5D utility score at 24 weeks).

When possible, certainty was rated in the context of the presence of an important (nontrivial) treatment effect; if this was not possible, certainty was rated in the context of the presence of any treatment effect (i.e., the clinical importance is unclear). In all cases, the target of the certainty of evidence assessment was based on the point estimate and where it was located relative to the threshold for a clinically important effect (when a threshold was available) or to the null. The target of the certainty of evidence assessment was the presence of a clinically important reduction of LDL-C (percent and absolute change in LDL-C) on thresholds informed from treatment guidelines and clinical expert opinion. Other targets for the certainty of evidence assessment were the presence or absence of any (non-null) effect for the proportion of patients achieving global lipid targets (i.e., percent change in Apo B, proportion of patients experiencing a 30% reduction in LDL-C, proportion of patients reaching LDL-C levels of 100 mg/dL or 70 mg/dL or less, the proportion of patients meeting US or EU apheresis criteria, and HRQoL measured by the EQ-5D).

Results of GRADE Assessments

Table 3 summarizes the detailed GRADE summary of findings for evinacumab versus placebo for outcomes in the pivotal ELIPSE trial of adolescent and adult patients with HoFH, while Table 4 summarizes the narrative GRADE summary of findings for evinacumab in the pediatric population of the CL-17100 trial and outcomes from the ELIPSE trial that were unable to be populated in the detailed summary of findings table.

Table 3: Detailed Summary of Findings for Evinacumab vs. Placebo for Adolescent and Adult Patients With HoFH (ELIPSE Trial)

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Placebo	Evinacumab	Difference		
Change in LDL-C							
Percent change from baseline in LDL-C, LSM Follow-up: 24 weeks	65 (1 RCT)	NA	1.9%	−47.1% (SE = 4.6)	−49.0% (−65.0 to −33.1)	Moderate[a]	Evinacumab likely results in a clinically important decrease (improvement) in LDL-C levels when compared with placebo.
Absolute change from baseline in LDL-C, LSM Follow-up: 24 weeks	65 (1 RCT)	NA	−2.6 mg/dL	−134.7 mg/dL (SE = 12.4)	−132.1 (−175.3 to −88.9)	Moderate[b]	Evinacumab likely results in a decrease (improvement) in LDL-C levels when compared with placebo.
Percent of patients with ≥ 30% reductions in LDL-C Follow-up: 24 weeks	65 (1 RCT)	RR: 5.0 (2.4 to 10.1)	4 of 22 (18 per 100)	36 of 43 (84 per 100)	650 more per 1,000 (450 more to 850 more)	Moderate[b]	Evinacumab likely results in a greater proportion of patients achieving 30% reductions in LDL-C levels when compared with placebo.
Percent of patients that meet US apheresis eligibility criteria Follow-up: 24 weeks	65 (1 RCT)	RR: 0.9 (0.7 to 1.1)	5 of 22 (23 per 100)	3 of 43 (7 per 100)	120 fewer per 1,000 (310 fewer to 60 more)	Low[b,c]	Evinacumab may result in fewer patients meeting US apheresis eligibility criteria compared with placebo. The clinical importance of the reduction is uncertain.
Percent of patients with LDL-C < 100 mg/dL (2.59 mmol/L) Follow-up: 24 weeks	65 (1 RCT)	RR: 1.4 (1.0 to 2.1)	5 of 22 (23 per 100)	20 of 43 (47 per 100)	230 more per 1,000 (10 fewer to 460 more)	Low[b,d]	Evinacumab may result in a greater proportion of patients achieving target LDL-C levels of < 100 mg/dL when compared with placebo.
Percent of patients that meet EU apheresis eligibility criteria Follow-up: 24 weeks	65 (1 RCT)	RR: 0.4 (0.2 to 0.8)	17 of 22 (77 per 100)	14 of 43 (33 per 100)	440 fewer per 1,000 (670 fewer to 210 fewer)	Low[b,d]	Evinacumab may result in fewer patients meeting EU apheresis eligibility criteria compared with

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Placebo	Evinacumab	Difference		
							placebo. The clinical importance of the reduction is uncertain.
Percent of patients with LDL-C < 70 mg/dL (1.81 mmol/L) Follow-up: 24 weeks	65 (1 RCT)	RR: 1.3 (1.1 to 1.6)	1 of 22 (5 per 100)	12 of 43 (28 per 100)	230 more per 1,000 (70 more to 390 more)	Low[b,e]	Evinacumab may result in a greater proportion of patients achieving target LDL-C levels of < 70 mg/dL when compared with placebo.
Change in Apo B							
Percent change from baseline in Apo B, LSM Follow-up: 24 weeks	65 (1 RCT)	NA	−4.5%	−41.4% (SE = 3.3)	−36.9 (−48.6 to −25.2)	Moderate[b]	Evinacumab likely results in a decrease (improvement) in Apo B levels when compared with placebo.
HRQoL							
Mean change from baseline in EQ-5D utility score Follow-up: 24 weeks	[redacted]	[redacted]	[redacted]	[redacted]	NR	Very low[b,e,f]	The evidence is very uncertain about the effects of evinacumab on HRQoL when compared with placebo.
Harms							
SAEs (safety end point) Follow-up: 24 weeks	Evinacumab: 44 Placebo: 21 (1 RCT; DBTP)	NA	0 (0 per 100)	2 (5 per 100)	NR	Low[g]	Evinacumab may result in more SAEs when compared with placebo.
SAEs (safety end point) Follow-up: 48 weeks	[redacted]	[redacted]	[redacted]	[redacted]	NA	Low[g]	Evinacumab may result in more SAEs vs. any comparator.
IRRs (safety end point) Follow-up: 24 weeks	Evinacumab: 44 Placebo: 21 (1 RCT; DBTP)	NA	1 (5 per 100)	3 (7 per 100)	NR	Low[g]	Evinacumab may result in more IRRs when compared with placebo.
IRRs (safety end point) Follow-up: 48 weeks	[redacted]	[redacted]	[redacted]	[redacted]	NA	Low[g]	Evinacumab may result in more IRRs vs. any comparator.

Apo B = apolipoprotein B; CI = confidence interval; DBTP = double-blind treatment period; IRR = infusion-related reaction; LDL-C = low-density lipoprotein cholesterol; LSM = least squares mean; LSMD = least squares mean difference; NA = not applicable; NR = not reported; OLTP = open-label treatment period; OR = odds ratio; RCT = randomized controlled trial; RD = risk difference; RR = risk ratio; SAE = serious adverse event; SE = standard error; vs. = versus.

Note: Study limitations (which refer to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias were considered when assessing the certainty of the evidence. All serious concerns in these domains that led to the rating down of the level of certainty are documented in the table footnotes.

[a]Rated down 1 level for serious imprecision. Although the sample size was adequate based on the sample size calculation for the primary end point, the small size raises concern about prognostic imbalance and potential overestimation of the true effect. Downgrading for risk of bias was considered due to the potential of spurious correlations when estimating percent change outcomes, but supportive evidence was sufficient to not downgrade.

[b]Rated down 1 level for serious imprecision. Based on the sample size (and baseline imbalances indicating randomization may not have ensured prognostic balance), rating down 2 levels would also be an option (−1 for imprecision and −1 for study limitations).

[c]This end point failed to meet statistical significance in the statistical hierarchy.

[d]This end point was not tested for superiority due to earlier failure of the statistical hierarchy. The potential for type I error is increased and the findings should be considered as supportive evidence.

[e]This end point was an exploratory outcome. The potential for type I error is increased and the findings should be considered as supportive evidence.

[f]Rated down 1 level for serious indirectness due to insufficient duration of follow-up for the outcome according to clinical expert input.

[g]Rated down 2 levels for very serious imprecision due to the absence of or very low number of events and small sample size.

Table 4: Narrative Summary of Findings for Evinacumab for Pediatric Patients With HoFH (CL-17100 Study)

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
Change in lipid parameters				
Percent and absolute change from baseline in LDL-C, LSM Follow-up: 24 weeks	14 (1 single-arm trial)	Percent CFB (part B): −48.32% (SD = 39.052) Absolute CFB (part B): −131.9 mg/dL (SD = 30.0)	Very low[a,b]	The evidence is very uncertain about the effects of evinacumab on reduction in LDL-C vs. any comparator.
Percent change from baseline in Apo B, LSM Follow-up: 24 weeks	14 (1 single-arm trial)	Percent CFB (part B): −41.32% (SD = 33.541)	Very low[a,b]	The evidence is very uncertain about the effects of evinacumab on reduction in Apo B vs. any comparator.
Harms				
SAEs (safety end point) Follow-up: 24 weeks	20 (1 single-arm trial)	Evinacumab: 1 (5 per 100)	Very low[a,c]	The evidence is very uncertain about the effects of evinacumab on SAEs vs. any comparator.
IRRs (safety end point) Follow-up: 24 weeks	20 (1 single-arm trial)	Evinacumab: 0 (0 per 100)	Very low[a,c]	The evidence is very uncertain about the effects of evinacumab on IRRs vs. any comparator.

Apo B = apolipoprotein B; HRQoL = health-related quality of life; IRR = infusion-related reaction; LDL-C = low-density lipoprotein cholesterol; LSM = least squares mean; SAE = serious adverse event; RCT = randomized controlled trial; SD = standard deviation.

Note: Study limitations (which refer to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias were considered when assessing the certainty of the evidence. All serious concerns in these domains that led to the rating down of the level of certainty are documented in the table footnotes. For single-arm trials, all serious concerns with study limitations (which refer to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias are documented in the table footnotes.

[a]In the absence of a comparator group, conclusions about efficacy relative to any comparator cannot be drawn and the certainty of evidence is started at very low and cannot be rated up.

[b]Rated down 2 levels for very serious imprecision due to the absence of or very low number of events and small sample size.

[c]Rated down 1 level for serious risk of bias due to potential for bias in favour of evinacumab arising from the open-label nature of the study and the subjective nature of the outcome. Rated down 1 level for serious imprecision as the small sample size raises concerns about prognostic imbalance and potential overestimation of the true effect. There is no known minimal important difference, and the target of certainty assessment was any effect.

Long-Term Extension Studies

Description of Studies

The CL-1719 study was a key long-term extension study submitted by the sponsor. The CL-1719 study is an ongoing long-term extension study evaluating the safety, tolerability, and efficacy of evinacumab in patients with HoFH, some of whom had previously participated in an evinacumab study (continued evinacumab) and some who were naive to evinacumab (new evinacumab). All patients received 15mg/kg of evinacumab intravenously, every 4 weeks, for 24 months. The study consisted of a run-in phase, a screening phase, a treatment period, and a 24-week follow-up period. [redacted].

Efficacy Results

[redacted]

Harms Results

[redacted]

Critical Appraisal

The lack of an internal comparator limits the interpretation of the treatment effect observed in the CL-1719 trial, as it is uncertain whether the magnitude of the effect observed for evinacumab as an adjunct to background LLT in patients continuing with evinacumab and new patients is attributed to evinacumab, due to variations in patient health status (continuing and new patients enrolled), residual effects from the use of evinacumab (for patients entering study from an evinacumab study, the impact of ongoing treatments on the effect of evinacumab efficacy), or other unidentified prognostic factors. The single-arm design does not allow for the differentiation of the symptoms of underlying HoFH from treatment-related AEs.

There were no established hypothesis tests and clear thresholds for the secondary variables assessed in the trial. A lack of hypothesis testing against clear thresholds reduces the internal validity of the efficacy findings as it introduces bias in the interpretation of the findings. The open-label design may have also introduced bias in the assessment of subjective outcomes such as the reporting of AEs. Missing data and the lack of methods to account for missing data in the analysis may have impacted the internal validity of the results. [redacted].

The CL-1719 study enrolled [redacted] based in Canada, although it was unclear if the results were generalizable to patients in Canada due to the small sample size and study design. Outcomes investigated were appropriate and reflective of current clinical practice. Follow-up duration was considered appropriate and more reflective of real-world practice. Concomitant medication and background LLT reported among patients [redacted]. These concomitant medications were also reflective of current clinical practice.

Indirect Comparisons

Description of Studies

No direct evidence comparing evinacumab to relevant comparators was available, and to support the pharmacoeconomic model for evinacumab, the sponsor submitted an indirect treatment comparison (ITC) that aimed to estimate the relative effect of evinacumab compared with relevant comparator treatments for adult and adolescent patients (aged 12 years and older) with HoFH to estimate the relative efficacy, safety, and tolerability of evinacumab compared with lomitapide, ezetimibe, evolocumab, and LDL apheresis.

The sponsor-submitted ITC first conducted a systematic literature review (SLR) to identify existing studies conducted in patients with HoFH. Patient-level data from the evinacumab and placebo arms of the ELIPSE trial were compared to aggregate data from the identified trials using Bucher ITCs and matching adjusted indirect comparison (MAIC) methods for the outcomes of percent reduction in LDL-C, proportion of patients with 50% reduction in LDL-C, proportion of patients who experienced any SAEs, and proportion of patients discontinuing the study due to any cause.

Efficacy Results

[redacted].

Critical Appraisal

The feasibility of conducting an ITC and subsequent analyses were informed by an SLR; however, no information was provided on the SLR methods with regard to the databases searched, the method of study selection or data extraction (i.e., duplicate reviewers), or quality assessment; thus, CADTH is unable to comment on whether appropriate methods were taken to identify studies for the inclusion in the ITCs. Two types of ITC were conducted: a MAIC and a Bucher ITC. Bucher ITCs were used for the comparison of evinacumab to evolocumab based on the connection of the studies via a placebo arm, [redacted].

The clinical experts consulted by CADTH could not confirm or refute that the prognostic factors and treatment effect modifiers consisting of [redacted] were the only relevant variables in this disease. The key limitation of the unanchored MAICs, which is a limitation

inherent to all unanchored MAICs, is that the assumption that all effect modifiers and prognostic factors are accounted for in the model is unlikely met.

[redacted]

The outcomes evaluated in the ITCs are relevant to the clinical management of HoFH. The sponsor conducted a Bucher ITC between evinacumab and evolocumab for the outcome of change from baseline in LDL-C, although no formal statistical analyses or adjustments were conducted; therefore, the results of this analysis should be interpreted with caution. MAICs were conducted for the outcomes of percent change from baseline in LDL-C and 50% reduction in LDL-C. Additional naive ITCs were conducted for safety outcomes including SAEs and proportion of patients discontinuing the studies due to any cause [redacted]; however, in all cases, 95% CIs were wide, suggesting notable imprecision in comparative efficacy estimates.

Studies Addressing Gaps in the Evidence From the Systematic Review

Description of Studies

The study by Stefanutti et al. (2022) assessed the long-term efficacy and safety of evinacumab in a cohort of patients with HoFH who were on and off background LDL apheresis, including other LLTs, in a real-world setting. Patients received evinacumab 15 mg/kg every 4 weeks for a duration of 24 months.

Efficacy Results

The mean percent reductions from baseline following the use of evinacumab and LDL apheresis treatment in LDL-C were −54.4%, −48.9%, −49.4%, and −46.8%, respectively, at 6, 12, 18, and 24 months ($P < 0.001$ for all compared with baseline). One patient discontinued LLT for hospitalization. Four patients experienced an LDL-C reduction of 50% or more, with 2 patients having on-treatment LDL-C levels less than 2.5 mmol/L (97 mg/dL).

Evinacumab (With or Without LDL Apheresis) Versus LDL Apheresis Alone

The LDL-C–lowering effect of evinacumab with or without background LDL apheresis treatment was greater than with LDL apheresis alone (i.e., without evinacumab treatment). With LDL apheresis alone, time-average LDL-C was reduced by 27.2% in the 6 patients who received LDL apheresis during the normal course of their therapy before initiation of evinacumab treatment.

Harms Results

There were no discontinuations due to severe AEs reported following the use of evinacumab. There were also no CV events observed during the 24-month follow-up and subsequent compassionate extension period (12 months) with evinacumab. There were no reports of symptoms related to common AEs (pharyngitis, nasal congestion, myalgia, diarrhea, and arthralgia). Overall, plasma aspartate aminotransferase (AST), alanine aminotransferase (ALT), and creatinine kinase concentrations for individual patients with HoFH remained stable with treatment with evinacumab.

Critical Appraisal

The lack of comparator and the open-label design of the prospective cohort were the main limitations of the study. There was no control group for comparison; thus, the benefit observed cannot be attributed to treatment with evinacumab. The sample size was considered too small to assess the magnitude of effects, and no sample size calculations were provided. There was little information provided related to the eligibility criteria of patients included in the study. There is a risk of detection bias for subjective outcome measurements such as AEs reporting due to the open-label nature of the study, given that patients and providers were aware of the treatment. The study duration (24 months) was considered long enough to assess the beneficial effects of evinacumab in the patient population. No HRQoL data were presented. It is uncertain whether evinacumab impacted patient outcomes in the real-world setting.

There is limited generalizability in terms of genetic confirmation of HoFH diagnosis. A clinical diagnosis criterion was not used in the study, which may not be reflective of Canadian practice guidelines. It was unclear what background LLTs were used alongside LDL apheresis.

Ethical Considerations

Patient group, clinician group, clinical expert, and drug program input gathered in the course of this CADTH review, as well as relevant literature, were reviewed to identify ethical considerations relevant to the use of evinacumab for the treatment of adult and pediatric patients aged 5 years and older with HoFH.

Ethical considerations identified in this review included those related to the following:

- **Diagnosis, treatment, and experiences of HoFH**: Ethical considerations in the context of HoFH highlighted the need for timely diagnosis and intervention to prevent early, harmful CV events and prolong survival. Current treatment options are inadequate in meeting the need for safe and effective therapies that can effectively manage harmful LDL-C levels resulting from HoFH, which are associated with premature CVD, and to alleviate the physical, emotional, and financial burdens experienced by patients and their families.
- **Clinical and economic evidence**: Clinical trial evidence indicated that evinacumab resulted in a statistically significant and clinically meaningful reduction in LDL-C compared to placebo and was well tolerated. However, the 24-week double-blind treatment duration within the trial was insufficient to assess long-term safety and efficacy, which limits assessment of clinical benefits and harms

associated with treatment as well as pharmacoeconomic assessment of cost-effectiveness. Moreover, the pivotal trial was not designed to assess other clinically relevant outcomes including CV-related outcomes, mortality, reduction in the need for and frequency of apheresis, or HRQoL.

- **Clinical decision-making for and implementation of evinacumab**: The use of evinacumab may present benefits to patients with HoFH as a potentially effective, tolerable, and less burdensome treatment to manage LDL-C levels and alleviate associated burdens and harms. Evinacumab may be more accessible and less burdensome for patients than treatment alternatives such as apheresis. Informed consent for pediatric patients requires careful consideration, especially because evinacumab is expected to be offered as a life-long therapy. Efforts to enhance access, including comanagement with primary care physicians and remote consultation, require consideration to address potential diagnostic and geographic barriers to equitable and timely access to evinacumab.
- **Health systems considerations**: Ethical considerations for health systems related to the implementation of evinacumab highlighted the challenges of funding decisions, considerations of distributive justice, assessments of opportunity costs for expensive drugs for rare diseases, and the continued need for more evidence for the use and implementation of evinacumab for pediatric and adult patients with HoFH.

Economic Evidence

Table 5: Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model
Target population	Patients aged 5 years and older with HoFH
Treatment	Evinacumab as an adjunct to diet and SOC
Dose regimen	15 mg/kg every 4 weeks
Submitted price	$10,164 per 345 mg vial $35,352 per 1,200 mg vial
Treatment cost	$460,839 per year, assuming a patient weight of 70 kg
Comparator	SOC, comprising a treatment mix of statins, ezetimibe, PCSK9 inhibitors and apheresis.
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (58 years)
Key data sources	ELIPSE trial to inform LDL-C treatment response Published literature to inform relationship between LDL-C and CV event risk

Component	Description
Key limitations	• In the sponsor's model, the treatment effect of evinacumab on CV outcomes was estimated based on the surrogate outcome of LDL-C lowering. The validity of using change in LDL-C as a surrogate for outcomes such as CV events in HoFH patients is not well established. The sponsor based this relationship on observed data from a meta-analysis of statin use, which may not be generalizable to the HoFH population. • Data used to estimate baseline CV event risk for the target population was derived from real-world evidence that is not reflective of the modelled population or current treatment regimens for patients with HoFH. As such, the impact of treatment on CV outcomes is uncertain. • The sponsor assumed that patients would maintain the treatment benefit of evinacumab observed in the trial for the entire model time horizon; however, the long-term efficacy of evinacumab is unknown. Given that the length of the trial was 24 weeks, considerable uncertainty remains with regard to the long-term efficacy and safety of evinacumab. • The assumptions of perfect vial-sharing and reduced treatment compliance were inappropriate and resulted in the underestimation of treatment costs for evinacumab. • The submitted model relied on assumptions around changes in apheresis use for patients who are being treated with evinacumab. However, the reduction in apheresis was linked to treatment costs but not to changes in treatment efficacy (i.e., LDL-C management). Further, the clinical experts consulted by CADTH indicated that there is uncertainty within the Canadian context regarding how apheresis use will be influenced by the introduction of evinacumab. • The submission did not adhere to good modelling practices, and the report was poorly organized and did not provide clear details of the methods. These aspects limited CADTH's ability to fully validate the submitted model. Further, clinical experts consulted by CADTH indicated that the model structure did not appropriately capture all relevant health events, including aortic valve disease.
CADTH reanalysis results	• To account for some of the key limitations, changes were made to derive the CADTH base-case analysis, which included: alternative assumptions about the relationship between LDL-C and CV event risk, and revisions to vial-sharing and treatment compliance. • CADTH was unable to address issues relating to the model structure, treatment effect waning, and use of apheresis. CADTH also notes that the true relationship between LDL-C and CV event risk remains unknown for patients with HoFH. • In the CADTH base case, the ICER for evinacumab plus SOC was $8,392,585 per QALY gained compared to SOC. A price reduction of approximately 98% (i.e., a drug cost of approximately $9,217 per year) would be required for evinacumab to be considered cost-effective at a $50,000 per QALY gained threshold.

CV = cardiovascular; HoFH = homozygous familial hypercholesterolemia; ICER = incremental cost-effectiveness ratio; LDL-C = low-density lipoprotein cholesterol; LY = life-year; PCSK9 = proprotein convertase subtilisin/kexin type 9; QALY = quality-adjusted life-year; SOC = standard of care.

Budget Impact

CADTH identified the following key limitations with the sponsor's analysis: the market shares for evinacumab were likely underestimated, the public drug coverage was likely underestimated, the drug acquisition costs for evinacumab were underestimated, and the inclusion of apheresis costs was inappropriate for the drug plan perspective. The CADTH reanalysis included: revising the market uptake and public drug coverage of evinacumab, accounting for drug wastage and complete compliance, and removing apheresis costs. Based on the CADTH reanalysis, the 3-year budget impact to the public drug plans of introducing evinacumab as an adjunct for the treatment of patients aged 5 years and older with HoFH is expected to be $54,834,025 (year 1: $14,031,446; year 2: $18,188,147; year 3: $22,614,433).

Request for Minor Reconsideration

The drug plans filed a request for minor reconsideration of the draft recommendation of evinacumab as an adjunct to diet and other LDL-C–lowering therapies for the treatment of adult and pediatric patients aged 5 years and older with HoFH. In their request, the drug plans identified the following issues:

- clarification on the definition of elevated LDL-C as it relates to patients with HoFH who are already receiving treatment with current standard of care, and what elevated LDL-C levels might be in these patients
- guidance on the method of calculating LDL-C in patients when triglyceride levels are too high and might not provide a measurable LDL-C level
- clarification on the definition of an adequate trial of standard of care therapies as it relates to dose and duration
- clarification on accessibility issues with PCSK9 inhibitors and the definition of "special access" for PCSK9 inhibitors
- guidance on the use of evinacumab as monotherapy if patients are unable to tolerate or their disease does not respond to all other accessible LLTs
- clarification on the definition of LDL-C reduction requirements for renewal, specifically, what LDL-C targets and/or thresholds are required to be met for continuation of funding following the initial authorization
- clarification on subsequent renewal situations where the LDL-C reduction is not maintained, but LDL-C levels remain below baseline.

In the meeting to discuss the drug plans' request for minor reconsideration, the CDEC subpanel considered the following sources of information:

- feedback and input from participating drug plans
- feedback from the sponsor
- information from the initial submission relating to the issues identified by the drug plans
- input from 2 clinical specialists with expertise in the diagnosis and management of patients with HoFH.

All stakeholder feedback that was received from clinician groups, patient groups, and the public drug programs in response to the draft recommendation is available on the CADTH website.

CDEC Information

Members of the Committee

Dr. James Silvius (Chair), Dr. Sally Bean, Mr. Dan Dunsky, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Mr. Morris Joseph, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Ms. Heather Neville, Dr. Danyaal Raza, Dr. Emily Reynen, and Dr. Peter Zed.

Meeting date: September 28, 2023

Regrets: None

Conflicts of interest: None

Minor reconsideration CDEC subpanel meeting date: December 22, 2023

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