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CADTH COMMON DRUG REVIEW

Pharmacoeconomic Review Report (Resubmission)

EVOLOCUMAB (REPATHA)

(Amgen Canada Inc.)

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

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Abbreviations

ACS	acute coronary syndrome
ASCVD	atherosclerotic cardiovascular disease
CDR	CADTH Common Drug Review
CHD	coronary heart disease
CPRD	Clinical Practice Research Database
CV	cardiovascular
CVD	cardiovascular disease
HF	heart failure
ICUR	incremental cost-utility ratio
IS	ischemic stroke
LDL-C	low-density lipoprotein cholesterol
PCSK9	pro-protein convertase subtilisin/kexin type 9
QALY	quality-adjusted life-years
QoL	quality of life
RR	relative risk
SOC	standard of care

Table 1: Summary of the Manufacturer's Economic Submission

Drug Product	Evolocumab (Repatha)
Study Question	From the perspective of a publicly funded health care payer, what is the incremental cost-effectiveness of evolocumab compared with available treatments for patients with ASCVD in Canada who cannot reach the recommended LDL-C target with SOC (medium- or high-intensity statins)?
Type of Economic Evaluation	Cost-utility analysis
Target Population	Patients with ASCVD
Treatment	Evolocumab 140 mg subcutaneously every 2 weeks plus SOC, defined as medium- or high-intensity statins
Outcome(s)	Quality-adjusted life-years
Comparator(s)	Medium- or high-intensity statins alone
Perspective	Canadian publicly funded health care payer
Time Horizon	Lifetime (40 years in the base case)
Results for Base Case	ICUR = $112,196/QALY compared with SOC
Key Limitations	CADTH Common Drug Review identified several key limitations with the submitted analysis: • The key limitation was that the manufacturer based its economic model on surrogate outcomes to predict long-term CV risk and mortality, while trial data that captured clinically important outcomes were available (in the FOURIER study). • It is not yet established that clinical efficacy persists over a patient lifetime given the relatively short duration of available trials. • Baseline risk was derived from the baseline characteristics of patients in the LDL-C LAPLACE-2 trial who experienced a prior CV event. This affected the generalizability of the results to the requested indication (ASCVD patients). • The treatment effects of LDL-C lowering on coronary heart disease event risk were derived from patient populations on less intensive statin therapy; this is not consistent with the increased intensity statin therapy observed in the patient populations in the clinical trials for evolocumab (LAPLACE-2). • Health state utilities were based on an industry-funded study that was conducted in the UK, despite the availability of Canadian studies with utility data for CV events. • The manufacturer's base-case analysis compared evolocumab with SOC, while ezetimibe was compared as part of a scenario analysis. Based on feedback from the clinical expert consulted for this review, patients with ASCVD who are on statins and require additional LDL lowering (as per indication) should arguably be on both a statin and ezetimibe. Therefore, the manufacturer's base-case analysis should have compared evolocumab + SOC to ezetimibe + SOC.
CDR Estimate(s)	Assuming a population with characteristics similar to the GLAGOV study population (which includes all ASCVD patients and is similar to the FOURIER study) and using information on clinically important outcomes observed in FOURIER, the following would be true: The ICUR for evolocumab plus SOC vs. SOC alone: $1,007,961 per QALY The ICUR for evolocumab plus SOC vs. ezetimibe plus SOC: $1,478,417 per QALY
Drug	Evolocumab (Repatha)
Indication	As an adjunct to diet and maximally tolerated statin therapy in adult patients with HeFH or clinical ASCVD who require additional lowering of LDL-C

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Reimbursement Request	For the treatment of patients as an adjunct to diet and maximally tolerated statin therapy in adult patients with clinical ASCVD who require additional lowering of LDL-C
Dosage Form(s)	Solution for subcutaneous injection
NOC Date	10-09-2015
Manufacturer	Amgen Canada Inc.

ASCVD = atherosclerotic cardiovascular disease; CDR = CADTH Common Drug Review; CV = cardiovascular; HeFH = heterozygous familial hypercholesterolemia; ICUR = incremental cost-utility ratio; LDL-C = low-density lipoprotein cholesterol; QALY = quality-adjusted life-year; SOC = standard of care; vs.= versus.

Executive Summary

Background

Evolocumab (Repatha) is indicated for use in adult patients with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (ASCVD) who require additional lowering of low-density lipoprotein cholesterol (LDL-C),as an adjunct to diet and maximally tolerated statin therapy.[1] Evolocumab is also indicated in patients who are 12 years of age and over with homozygous familial hypercholesterolemia as an adjunct to diet and other LDL-C-lowering therapies.[1] The dosage form is 1 mL of solution (140 mg/mL evolocumab) in a single-use, pre-filled auto-injector that is intended to be patient self-administered subcutaneously.[1] At the submitted price of $279.36 per 140 mg dose, at the recommended dose of 140 mg every 2 weeks, the annual cost of evolocumab is $7,263.[1,2]

The submitted product monograph for evolocumab includes a 420 mg once-monthly dosage regimen using three injections of 140 mg. Based on the product monograph, and as confirmed by the clinical expert, the 420 mg monthly dose can be administered using three injections of the 140 mg/mL pre-filled auto-injector.[1] The 420 mg monthly dosage might be preferred by some patients and physicians to improve patient compliance, and is supported by the results of the submitted clinical trials for evolocumab efficacy (LDL-C Assessment with PCSK9 Monoclonal Antibody Inhibition Combined with Statin Therapy [LAPLACE-2], RUTHERFORD-2, and GAUSS-2)[3-5] that were designed to include the 420 mg monthly regimen and which concluded that efficacy between the 140 mg every two weeks and the 420 mg monthly regimens was similar. By providing evolocumab at a monthly dose of 420 mg, the annual cost of evolocumab increased to $10,057.[2]

Evolocumab was previously reviewed by the CADTH Common Drug Review (CDR) and received a positive listing recommendation from the CADTH Canadian Drug Expert Committee in January 2016 as an adjunct treatment to diet and maximally tolerated statin therapy in adult patients with HeFH who require additional lowering of LDL-C, under the condition that the drug plan cost of a dosage regimen of 420 mg of evolocumab once per month does not exceed the drug plan cost of a dosage regimen of 140 mg of evolocumab every two weeks.[6]

The manufacturer submitted a cost-utility analysis of evolocumab as add-on to medium- or high-intensity statins in patients with ASCVD compared with medium- or high-intensity statins alone (i.e., standard of care [SOC]). The manufacturer defined medium-intensity statin therapy as rosuvastatin at 5 mg daily, while high-intensity statin therapy was defined as rosuvastatin at 40 mg daily. Baseline cardiovascular (CV) risk was based on the Clinical

Practice Research Database (CPRD), a retrospective observational cohort study in multiple UK cohorts, and LDL-C levels from the study population (LAPLACE-2).[1,3]. The treatment effects were assessed by combining the treatment efficacy in terms of (absolute) LDL-C lowering from the evolocumab trial (LAPLACE-2)[3] and the results from a meta-analysis of 26 randomized clinical trials of statins that estimated the absolute LDL-C lowering impact on CV event outcomes (Baigent et al. 2010).[7] The analyses were conducted from the perspective of a Canadian health care payer assuming a lifetime horizon (40 years).

In contrast to the previous submission, the efficacy of ezetimibe in lowering LDL-C was assessed based on the LAPLACE-2 study instead of the GAUSS-2 trial.[3,5] The treatment effects of evolocumab on CV risk and CV mortality were estimated using the surrogate outcome of LDL-C reduction from the phase III clinical trials (LAPLACE-2).[3] The treatment effects were combined with the results from a meta-analysis of 26 randomized clinical trials of statins that estimated absolute LDL-C lowering impact on CV event outcomes (Baigent et al. 2010).[7] Adverse events were not modelled, as clinical trials indicated that evolocumab was well tolerated.[1] Other inputs, such as costs and utilities, were obtained from published literature.[1] Costs and outcomes beyond one year were discounted at 1.5%.[1]

In the present submission for evolocumab, the manufacturer reported an incremental cost-utility ratio (ICUR) of $112,196 per QALY when compared with SOC in the base-case analysis. The scenario analysis that compared evolocumab with ezetimibe as add-ons to SOC resulted in an ICUR of $158,855 per QALY. Based on the manufacturer's probabilistic sensitivity analyses, in 15% of simulations, the ICUR is less than $100,000 per QALY for evolocumab + SOC compared with SOC alone, while for the probabilistic analyses comparing evolocumab + SOC to ezetimibe + SOC, none of the simulations resulted in an ICUR of less than $100,000 per QALY.

Summary of Identified Limitations and Key Results

CDR identified several key limitations with the manufacturer's submitted analysis, the key one being that the economic model used the surrogate outcome of LDL-C reduction to predict long-term CV risk and mortality by assuming a relationship similar to that observed with statins. While the use of a validated surrogate outcome itself is not inappropriate, using a surrogate outcome is questionable where clinically important outcomes are available (e.g., the Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk study [FOURIER]). Furthermore, findings from the FOURIER study suggest that the modelling of efficacy using surrogate outcomes, rather than available data from a clinical trial, overestimates the relative effectiveness of evolocumab considerably. Also, given the relatively short duration of available trials, the durability of the treatment effect with evolocumab has not been established (i.e., there is no information to suggest that the clinical effect will persist over a patient lifetime). Other limitations CDR noted include that baseline risks and utilities were derived from UK cohorts as well as from the baseline characteristics reported in the LAPLACE-2 study, which might not be generalizable to the Canadian population with ASCVD. Finally, CDR noted that the manufacturer's base-case analysis did not include ezetimibe as a comparator in the base-case analysis, despite feedback from the clinical expert consulted for this review that patients with ASCVD who are on statins and require additional LDL lowering (as per indication) should be on both a statin and ezetimibe.

Other limitations that CDR identified for this resubmission were also noted in the previous submission for evolocumab; they include the impact of LDL-C lowering in reducing coronary heart disease (CHD) death risk, model time horizon and treatment duration, and uncertainty in the health state utility values.

CDR attempted to address these limitations, where a population with characteristics similar to that of the Global Assessment of Plaque Regression with PCSK9 Antibody as Measured by Intravascular Ultrasound (GLAGOV) study population (which itself was similar to that of FOURIER) was considered, and the relative risks (RRs) of clinically important outcomes observed in FOURIER replaced the surrogate outcomes. In the CDR reference case, the ICUR for evolocumab + SOC versus SOC is $1,007,961 per QALY. Using the same assumptions as above, the ICUR for evolocumab + SOC versus ezetimibe + SOC is $1,478,417 per QALY.

Conclusions

The key limitation of this submission was how the clinical effectiveness for evolocumab versus medium- or high-intensity statins was modelled in the economic analysis: the surrogate outcome of LDL-C reduction was used to predict long-term CV risk and mortality when trial data were available. Another limitation was the baseline risk derived from a study that might not be generalizable to the Canadian population. These key limitations resulted in uncertainty with evolocumab's cost-effectiveness versus statins in patients with ASCVD. CDR addressed this limitation with reanalyses that utilized data on clinically important outcomes from the FOURIER trial. Other limitations assessed were the modelled treatment duration and time horizon, health state utility values, and the impact of lowering the surrogate outcomes on CV death.

CDR reanalyses to address the identified limitations with the manufacturer's economic analysis showed that results were sensitive to evolocumab efficacy when based on clinically important outcomes from trial data rather than surrogate outcomes: the ICURs for evolocumab added to statins — when compared with either background statins alone or ezetimibe plus background statins — were more than $1 million per QALY.

A price reduction of more than 90% would be required for the ICUR for evolocumab to fall to $50,000 per QALY when compared with statins alone or ezetimibe plus statins.

Summary of the Manufacturer's Pharmacoeconomic Submission

The manufacturer submitted a cost-utility analysis comparing evolocumab plus medium- or high-intensity statins with medium- or high-intensity statins alone in patients with known atherosclerotic cardiovascular disease (ASCVD).[1] The time horizon was a patient lifetime (40 years) with an annual cycle length; the analysis adopted the Canadian public payer perspective.[1] The following health states were used in the model: established cardiovascular (CV) disease, acute coronary syndrome (ACS), ischemic stroke (IS), heart failure (HF), post-ACS, post-IS, post-HF, CV death, and non-CV death (Figure 1).[1] The proportion of patients in each initial health state was based on the trial population (LAPLACE-2) in the base case.[1] All patients in the model started in the established CV death state or the post-CV event state, and could remain in the same health state, transition to a new CV event health state, or die. Once patients experienced a new CV event and had moved to the post-CV event state, they could not return to a less severe health state. The model captures multiple combined post-CV disease health states to track patients' disease history, allowing for multiple CV events to occur over time. Face validity, internal validity, cross-validation, and external validity comparing the Cholesterol Treatment Trialists' Collaboration RRs as well as the predicted RR of CV events with evolocumab + SOC with those observed in the Open-Label Study of Long-Term Evaluation against LDL Cholesterol (OSLER) trial (2015)[8] were performed (only RRs were examined; validation of baseline event rates were not commented on).[1]

Transition probabilities for CV risks and CV deaths for the SOC group, stratified by age group and diabetes status, were estimated from the CPRD, a retrospective observational cohort study to estimate event rates in multiple cohorts in the UK.[1] Baseline event rates were also modified by the baseline low-density lipoprotein cholesterol (LDL-C) obtained from the study population (LAPLACE-2 in the manufacturer reference case).[1,3] Non-CV deaths were estimated by subtracting CV deaths from all-cause deaths in the Canadian Life Tables.[1] The relationship between LDL-C reduction (as observed in LAPLACE-2) and the corresponding change in CV risk was estimated assuming that the relationship is the same as that observed with statins (from a meta-analysis [Baigent]).[1,7] Adverse events (AEs) were not modelled, as findings from phase III trials (LAPLACE-2, OSLER, and GLAGOV) indicated that evolocumab was well tolerated.[3,8,9] Utilities for each health state were obtained from a UK study, as Canadian data did not provide information on all health states in the model (Matza et al. 2015).[10]

Drug costs were obtained from the manufacturer based on a dosage of 140 mg every two weeks (note: the manufacturer did not seek reimbursement for the 420 mg once-monthly dosage). The costs of statins were obtained from the Ontario Drug Benefit Formulary, and the least expensive alternative (Rosuvastatin, 40 mg and 5 mg) within each statin intensity category was chosen.[1] Initial and subsequent costs for CV events were estimated from Canadian published studies (Goeree, Mittmann, Blackhouse, and Smolderen).[11-14] The cost for a combined health state was defined by the maximum of the cost for the individual health states.[1]

Information on the Pharmacoeconomic Submission

Manufacturer's Base Case

In the reference case, the manufacturer reported that evolocumab + SOC is associated with an additional 1.03 quality-adjusted life-years (QALYs) compared with SOC, and 0.72 QALY compared with ezetimibe + SOC, an incremental cost of $115,055 versus SOC and $113,648 versus ezetimibe + SOC, resulting a cost per QALY of $112,196 versus SOC, and $158,855 versus ezetimibe + SOC (Table 2).

Table 2: Results of the Manufacturer's Base-Case Analysis

	Evolocumab + SOC (a)	SOC (b)	Difference (a – b)	Ezetimibe + SOC (c)	Difference (a – c)
QALYs	11.78	10.76	1.03	11.07	0.72
Cost ($)					
Drug acquisition costs	117,109	1,478	115,631	3,301	113,808
CVD events (acute)	19,576	27,864	–8,288	25,111	–5,535
CVD event (long-term)	74,436	66,724	7,712	69,061	5,375
Total costs	211,121	96,066	115,055	97,473	113,648
ICUR ($/QALY)			112,196		158,855

CVD = cardiovascular disease; ICUR = Incremental cost-utility ratio; LY = life-years; QALY = quality-adjusted life-years; SOC = standard of care.

Source: Manufacturer pharmacoeconomic submission.[1]

Summary of Manufacturer's Sensitivity Analyses

Uncertainty was addressed using Monte Carlo simulation and one-way deterministic sensitivity analyses, which varied model parameters by using alternative values. A series of one-way sensitivity analyses were conducted by the manufacturer, which covered discounting on outcomes or costs (0, 5%); the effect of LDL-C lowering on coronary heart disease (CHD) death (RR 0.74 to 0.87); treatment duration (5 to 75 years); the effect of LDL-C lowering on IS death (RR 0.77 to 1); the effect of LDL-C lowering on HF (RR 0.71 to 1); and the effect of LDL-C lowering on IS (RR 0.5 to 0.95).

The reference case result for evolocumab + statins versus SOC (statins alone) was $112,196 per QALY. The following parameters increased or decreased the incremental cost per QALY gained by more than 25%:

- a discount rate of 5% on outcomes, cost per QALY: $207,671
- a discount rate of 5% on costs, cost per QALY: $77,913
- the effect of LDL-C lowering on CHD death, cost per QALY: $147,553
- a treatment duration of five years, cost per QALY: $143,846.

Based on the manufacturer's probabilistic sensitivity analyses, in 15% of simulations, the ICUR was less than $100,000 per QALY for evolocumab + SOC compared with SOC alone. In the probabilistic analyses comparing evolocumab + SOC to ezetimibe + SOC, 0% of the simulations resulted in an ICUR less than $100,000 per QALY.

The manufacturer also provided scenario analyses for comparisons with ezetimibe + SOC and alirocumab + SOC that considered a population similar to the GLAGOV study:

- versus ezetimibe + SOC: $158,855 per QALY
- versus alirocumab + SOC: 75 mg ($9,831 per QALY), 150 mg ($9,995 per QALY)
- using GLAGOV population: $164,599 per QALY.

Limitations of Manufacturer's Submission

Use of Surrogate Outcomes

The treatment effect of evolocumab on CV events and mortality was estimated based on the association between reduction of LDL-C and CV risk and mortality observed with statins from the Cholesterol Treatment Trialists' Collaboration meta-analysis (Baigent 2010).[7] No justification is given for this assumption. It is not appropriate to conduct economic analyses using surrogate outcomes extrapolated and modelled to estimate clinically relevant outcomes when trial data on clinically relevant outcomes are available (e.g., in FOURIER).[15] Further, the FOURIER trial CV event RR per mmol/L LDL-C reduction was markedly lower than predicted; the clinical expert indicated that only a 15% to 20% CV risk reduction was observed in the trial, while a 50% CV risk reduction was predicted based on LDL-C lowering (under the assumption of a similar relationship as observed with statins). The observed RRs from FOURIER were used in the CADTH Common Drug Review (CDR) reanalysis (with difficulty, as the model was not designed to use this data).

Uncertainty Surrounding the Efficacy of Evolocumab in Reducing Cardiovascular Event Risk

The manufacturer modelled the impact of LDL-C reduction by evolocumab on CV event risks as per the results of the meta-analysis by Baigent et al. (2010)[7] of more than 170,000 patients in 26 trials of statins.[1] The manufacturer's pharmacoeconomic submission indicated that the results from Baigent et al. (2010)[7] for "more vs. less statins" patient populations were incorporated in the model, as such populations and treatments were considered by the manufacturer to resemble the target populations for evolocumab in this analysis.[1] Upon verification of the included inputs, CDR noted that the rate ratios from Baigent et al. (2010)[7] may not have consistently represented similar populations. While estimates for ACS and IS were from the "more vs. less statin" studies, the estimates for CHD and fatal IS were derived from the overall populations included in the meta-analysis, despite a reported CHD death rate ratio in the "more vs. less statin" group.

Baseline Risk of Population

The transition probabilities obtained from the CPRD might not be applicable to the Canadian population or patients with ASCVD.[1] Furthermore, baseline risk was modified by the difference of the initial LDL-C of the trial population (LAPLACE-2) and that of the CPRD.[1,3] It is not clear if the baseline risk in the model approximates the eligible Canadian population. If the baseline risk is overestimated, this may overestimate the absolute benefit of evolocumab.

Inappropriate Comparator in the Base-Case Analysis

The manufacturer's base-case analysis compared evolocumab with SOC alone (medium- or high-intensity statins), but only included ezetimibe in a scenario analysis. According to the clinical expert consulted for this review, patients with ASCVD who are on a statin and require additional LDL lowering (as per indication) should arguably be on both a statin and ezetimibe. In the scenario analysis conducted by the manufacturer, the efficacy estimates on LDL-C reduction for ezetimibe were obtained from the LAPLACE-2 trial (Robinson et al. 2014)[3] despite the availability of observed LDL-C reduction for evolocumab versus ezetimibe + SOC and evolocumab versus SOC in the FOURIER trial.[15]

Utilities

The model used a UK quality of life (QoL) study for all health states (established CVD, ACS, IS, HF, and post-CV event states), which might not be applicable to the Canadian population.[10] A range of QoL inputs obtained from another Canadian study (Saw et al. 2016) were tested.[16]

Model Horizon, Treatment Duration, and Efficacy Over Time

The manufacturer's reference case assumed a lifetime horizon of 40 years. The average patient age was 60 (LAPLACE-2) and 63 (FOURIER); no model validation was performed to indicate that modelled survival approximates observed survival in treatment-eligible cohorts.[3,15] Additionally, it is plausible that treatment may not be administered over the long term. It is notable that approximately 45% of incremental QALYs with evolocumab are realized after 20 years. Finally, there is lack of evidence on the long-term efficacy of evolocumab, given the short durations of available trials. A shorter time horizon (20 years) and shorter treatment duration (20 years) were tested to evaluate.

CADTH Common Drug Review Reanalyses

CDR considered the following analyses to address the limitations identified above:

1. **Utilities**. The upper and lower confidence intervals (CIs) for each of the health states from the UK study were assessed; utilities (as well as the 95% CI) from a Canadian publication were also assessed (see Table 16 in Appendix 5 for background information). As per Table 3, using alternate utility scores had a relatively small impact on model results.
2. **Different trial population**. The LDL-C of patients in the GLAGOV study was similar to that observed in FOURIER; patients in LAPLACE-2 had a higher LDL-C than patients in both of these studies (see Table 17 in Appendix 5). As such, the baseline characteristics of LAPLACE-2 may be more suitable. Using a population based on the GLAGOV study population (with a lower modelled baseline risk due to lower initial LDL-C) results in a lower absolute benefit and a larger ICUR (Table 3).
3. **Incorporation of RRs reported from FOURIER**. Although it was technically challenging, CDR attempted to integrate FOURIER findings into the manufacturer model (see Appendix 5). Lower relative benefit led to less incremental QALYs and a larger ICUR than the manufacturer reference case.

4. **Model duration and treatment duration**. When model duration was shortened to 20 years, absolute benefits decreased relative to costs (approximately 45% of incremental QALYs are realized after 20 years); thus, the ICURs increased. When treatment duration was truncated to 20 years, the ICUR increased slightly. If long-term efficacy attenuates over time, the ICUR will be even higher (not modelled).

5. **CDR reference case.** This reference case used RR informed by the FOURIER study results and the GLAGOV population. Sensitivity analysis on this reference case was conducted (not shown). In all analyses, the ICUR for evolocumab is greater than $500,000 per QALY (versus SOC as well as SOC + ezetimibe). A sensitivity analyses was conducted on the CDR reference case (see Appendix 5). One sensitivity analysis explored the impact on results if evolocumab has a benefit on CV death (see Appendix 5); ICUR ranges from $209,000 to 278,000 per QALY versus SOC and $299,000 to 397,000 per QALY versus ezetimibe +SOC).

Table 3: CADTH Common Drug Review Reanalyses

	Description	Evolocumab + SOC Versus SOC			Evolocumab + SOC Versus Ezetimibe + SOC		
		Incremental Cost ($)	Incremental QALYs	ICUR ($/QALY)	Incremental Cost ($)	Incremental QALYs	ICUR ($/QALY)
	Manufacturer's base case (LAPLACE-2 population)[1]	115,055	1.03	112,196	113,648	0.72	158,855
1	**Utilities**						
1a	CI (Matza et al.)[10]	115,055	0.99 to 1.05	109,839 to 115,654	113,648	0.69 to 0.73	155,373 to 164,899
1b	Canadian study (Saw et al.)[16]	115,055	0.86 to1.20	95,828 to 134,034	113,648	0.60 to 0.84	135,601 to 189,000
2	**Trial population characteristics**						
	GLAGOV (as in manufacturer's sensitivity analysis)[1]	129,341	0.79	164,599	128,110	0.53	242,475
3	**Observed RR from FOURIER**	102,832	0.13	792,576	102,256	0.09	1,134,553
4	**Model duration and treatment duration**						
4a	Model duration (20 years)	95,647	0.57	167,132	95,160	0.39	242,345
4b	Treatment duration (20 years)	115,055	0.85	115,090	96,971	0.59	164,669
5	**Plausible reference case (2 & 3)**	**122,841**	**0.12**	**1,007,961**	**121,737**	**0.08**	**1,478,417**

CI = confidence interval; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-years; RR = relative risk; SOC = standard of care; vs. = versus.

Table 4: CADTH Common Drug Review Reanalysis Price Reduction Scenarios

ICURs of Submitted Evolocumab + SOC Versus SOC		
Price	**Base-Case Analysis Submitted by Manufacturer ($/QALY)**	**Reanalysis by CDR (Based on Plausible Reference Case) ($/QALY)**
Submitted	112,196	1,007,961
10% reduction	100,933	904,781
20% reduction	89,670	801,600
25% reduction	84,038	750,010
30% reduction	78,407	698,420
40% reduction	67,144	595,240
50% reduction	55,881	492,059
55.22% reduction	**50,002**	438,199
60% reduction	44,618	388,879
70% reduction	33,356	285,699
80% reduction	22,093	182,518
90% reduction	10,830	79,338
92.85% reduction	7,620	**49,932**
95% reduction	5,198	27,748

CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; SOC = standard of care.

Table 5: CADTH Common Drug Review Reanalysis Price Reduction Scenarios

ICURs of Submitted Evolocumab + SOC Versus Ezetimibe + SOC		
Price	**Base-Case Analysis Submitted by Manufacturer ($/QALY)**	**Reanalysis by CDR (Based on Plausible Reference Case) ($/QALY)**
Submitted	158,855	1,478,417
10% reduction	142,711	1,325,706
15% reduction	134,639	1,249,350
20% reduction	126,567	1,172,995
25% reduction	118,495	1,096,639
30% reduction	110,423	1,020,283
40% reduction	94,279	867,572
50% reduction	78,134	714,861
60% reduction	61,990	562,149
67.43% reduction	***49,995***	448,685
70% reduction	45,846	409,438
80% reduction	29,702	256,727
90% reduction	13,558	104,016
93.54% reduction	7,842	***49,956***
95% reduction	5,485	27,660

CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; SOC = standard of care.

Issues for Consideration

- The economic submission did not assess the cost-effectiveness of evolocumab as a monotherapy for patients who were statin intolerant, but there is a possibility of use in this patient population. Using evolocumab instead of a statin is not examined in this analysis, but may have significant implications for cost as well as total CV risk reduction. Furthermore, statin intolerance is not clinically well defined; there is the possibility that patients who could safely be treated with statin medications may be treated with evolocumab instead due to perceived “intolerance” (Gupta et al. 2017).[17]
- Although the manufacturer did not seek reimbursement for the 420 mg once-monthly dosage, this dosage can be administered using three injections of the 140 mg/mL pre-filled auto-injector. This scenario, which significantly increases drug acquisition costs, is explored under the CDR reanalyses sensitivity analyses.
- Perceived intolerance to statin medications (as above) may lead to suboptimal use and up-titration of statins (and less LDL-C lowering). As the indication is based on LDL-C levels, this may lead to a larger number of patients being eligible for treatment with evolocumab, with attendant budget implications.[18] While not formally examined, given that the clinical benefit of LDL-C reduction appears to be greater with statins than with evolocumab, this scenario may also lead to suboptimal patient outcomes.

Patient Input

Input was received from the Cardiac Health Foundation of Canada. The patient group noted that respondents expected evolocumab to reduce cholesterol levels with minimal side effects — particularly the side effects experienced with statins, such as muscle function loss or muscle weakness. The manufacturer’s cost-utility analysis was based on the clinical efficacy of evolocumab on lowering LDL- C, but did not include the incidence, cost, or health-related QoL effects of AEs associated with statins or evolocumab therapy. Patients also indicated that their QoL was affected because they were anxious about having another CV event; while anxiety was not specifically modelled, the disutility of CV events (acute or long-term) was included in the model.

Conclusions

The key limitation of this submission was how the clinical effectiveness for evolocumab versus medium- or high-intensity statins was modelled in the economic analysis: by using the surrogate outcome of LDL-C reduction to predict long-term CV risk and mortality when trial data were available. Another limitation was the baseline risk derived from a study that might not be generalizable to the Canadian population. These key limitations resulted in uncertainty regarding evolocumab's cost-effectiveness versus statins in patients with ASCVD. CDR addressed this limitation with reanalyses that utilized data on clinically important outcomes from the FOURIER trial. Other limitations assessed were the modelled treatment duration and time horizon, health state utility values, and the impact of lowered surrogate outcomes on CV death.

CDR reanalyses to address the limitations identified in the manufacturer's economic analysis showed that results were sensitive to evolocumab efficacy when based on clinically important outcomes from trial data rather than on surrogate outcomes: the ICURs for evolocumab added to statins, when compared with either background statins alone or ezetimibe plus background statins, were more than $1 million per QALY.

A price reduction of more than 90% would be required for the ICUR for evolocumab to fall to $50,000 per QALY when compared with statins alone or ezetimibe plus statins.

Appendix 1: Cost Comparison

The comparators presented in Table 6 have been deemed appropriate by clinical experts. Comparators may be recommended (appropriate) practice versus actual practice. Comparators are not restricted to drugs but may be devices or procedures. Costs are manufacturer list prices, unless otherwise specified. Existing product listing agreements are not reflected in the table and, as such, the prices shown may not represent the actual costs to public drug plans.

Table 6: CADTH Common Drug Review Cost Comparison Table for Evolocumab

Drug/Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Average Daily Drug Cost ($)	Average Annual Drug Cost ($)
Evolocumab (Repatha)	140 mg/mL	pre-filled glass syringe	279.3600[a] per 140 mg/mL dose	140 mg SC injection every 2 weeks or 420 mg every month	19.90 to 27.55	7,263 to 10,057
HMG-CoA Reductase Inhibitors (Statins)						
Rosuvastatin calcium (Crestor and generics)	5 mg 10 mg 20 mg 40 mg	tab	0.2311 0.2437 0.3046 0.3582	10 to 40 mg daily	0.24 to 0.36	88.95 to 130.74
Atorvastatin calcium (Lipitor and generics)	10 mg 20 mg 40 mg 80 mg	tab	0.2615 0.3268 0.3513 0.3513	10 to 80 mg at bedtime	0.26 to 0.35	95.45 to 128.22
Fluvastatin sodium (Lescol and generics)	20 mg 40 mg	cap	0.2202 0.3092	20 to 40 mg at bedtime	0.22 to 0.31	80.37 to 112.86
Fluvastatin sodium (Lescol XL)	80 mg	tab	1.5960	80 mg daily	1.60	582.54
Lovastatin (Mevacor and generics)	20 mg 40 mg	tab	0.4919 0.8985	20 to 80 mg at bedtime	0.49 to 0.90	179.54 to 655.91
Pravastatin sodium (Pravachol and generics)	10 mg 20 mg 40 mg	tab	0.4050 0.4778 0.5755	10 to 40 mg at bedtime	0.41 to 0.58	147.83 to 210.06
Simvastatin (Zocor and generics)	5 mg 10 mg 20 mg 40 mg 80 mg	tab	0.1534 0.3035 0.3751 0.3751 0.3751	10 to 80 mg at bedtime	0.30 to 0.38	110.78 to 136.91
Cholesterol Absorption Inhibitors						
Ezetimibe (Ezetrol)	10 mg	tab	0.3260	10 mg daily	0.33	118.99

SC = subcutaneous.

[a] Manufacturer's submitted market price.[1]

Source: Ontario drug benefit formulary, May 2017, unless indicated otherwise; figures do not include dispensing fees.[19]

Appendix 2: Summary of Key Outcomes

Table 7: When Considering Only Costs, Outcomes, and Quality of Life, How Attractive Is Evolocumab + SOC Relative to SOC?

Evolocumab + SOC Versus SOC	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	N/A
Costs (total)				X		
Drug treatment costs alone					X	
Clinical outcomes		X				
Quality of life		X				
Incremental CE ratio or net benefit calculation	Manufacturer's reference case: $112,196/QALY CDR reference case: $1,007,961/QALY					

CDR = CADTH Common Drug Review; CE = cost-effectiveness; QALY = quality-adjusted life year; SOC = standard of care.

Table 8: When Considering Only Costs, Outcomes, and Quality of Life, How Attractive Is Evolocumab + SOC Relative to Ezetimibe + SOC?

Evolocumab + SOC Versus Ezetimibe + SOC	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	N/A
Costs (total)				X		
Drug treatment costs alone					X	
Clinical outcomes		X				
Quality of life		X				
Incremental CE ratio or net benefit calculation	Manufacturer's scenario analysis: $158,855/QALY CDR scenario analysis: $1,478,417/QALY					

CDR = CADTH Common Drug Review; CE = cost-effectiveness; QALY = quality-adjusted life year; SOC = standard of care.

Appendix 3: Additional Information

Table 9: Submission Quality

	Yes/ Good	Somewhat/ Average	No/ Poor
Are the methods and analysis clear and transparent?	X		
Comments Reviewer to provide comments if checking “no”	None		
Was the material included (content) sufficient?		X	
Comments Reviewer to provide comments if checking “poor”	New trial data (FOURIER) was not included in the economic model.[15]		
Was the submission well organized and was information easy to locate?	X		
Comments Reviewer to provide comments if checking “poor”	Missing page numbers in the report		

Table 10: Authors’ Information

Authors of the pharmacoeconomic evaluation submitted to CADTH Common Drug Review			
☐ Adaptation of global model/Canadian model done by the manufacturer ☒ Adaptation of global model/Canadian model done by a private consultant contracted by the manufacturer ☐ Adaptation of global model/Canadian model done by an academic consultant contracted by the manufacturer ☐ Other (please specify)			
	Yes	**No**	**Uncertain**
Authors signed a letter indicating agreement with entire document	X		
Authors had independent control over the methods and right to publish analysis		X	

Appendix 4: Summary of Other Health Technology Assessment Reviews of Drug

Table 11: Other Health Technology Assessment Findings

	NICE (June 2016)[20]	NCPE (October 2016)[21]
Treatment	Evolocumab + statins	
Price	Confidential	Confidential
Similarities with CDR submission	Lifetime Markov model in reducing CVD through LDL-C reduction	
Differences with CDR submission	Different discount rates, utilities, costs, and patient population (non-familial hypercholesterolemia)	
Manufacturer's results	£46,005 to £74,331 (CAD $79,115 to $127,827) per QALY vs. placebo[a]	€ 194,519 (CAD $294,351)[b] per QALY (LAPLACE-2) vs. placebo € 290,037 (CAD $426,964)[b] per QALY vs. ezetimibe
Issues noted by the review group	Likely overestimation for the risk of CVD based on the Benn et al. RR; uncertainty about the relationship between LDL-C reduction and reductions in CV events	Concerns in relation to the selection and subsequent treatment of the CV events
Results of reanalyses by the review group (if any)	£45,439 to £69,249 per QALY vs. placebo	€ 276,173 per QALY vs. placebo € 406,067 per QALY vs. ezetimibe
Recommendation	Evolocumab is recommended as an option for treating primary hypercholesterolemia or mixed dyslipidemia only if: • The dosage is 140 mg every 2 weeks. • Low-density lipoprotein concentrations are persistently above the thresholds in the guidance despite maximally tolerated lipid-lowering therapy. That is, either the maximum dose has been reached, or further titration is limited by intolerance (as defined in NICE's guideline on familial hypercholesterolemia). • The company provides evolocumab with the discount agreed to in the patient access scheme.	Not recommended for reimbursement. Evolocumab was not considered cost-effective for the treatment of primary hypercholesterolemia and mixed dyslipidemia.

CDR = CADTH Common Drug Review; CV = cardiovascular; CVD = cardiovascular disease; LDL-C = low-density lipoprotein cholesterol; NCPE = National Centre for Pharmacoeconomics; NICE = National Institute for Health and Care Excellence; QALY = quality-adjusted life-year; RR = relative risk; SOC = standard of care; vs. = versus.

[a] £1 = CAD$1.7197 (Bank of Canada historical closing rate, October 31st, 2016). (www.bankofcanada.ca/rates/exchange/legacy-noon-and-closing-rates/).

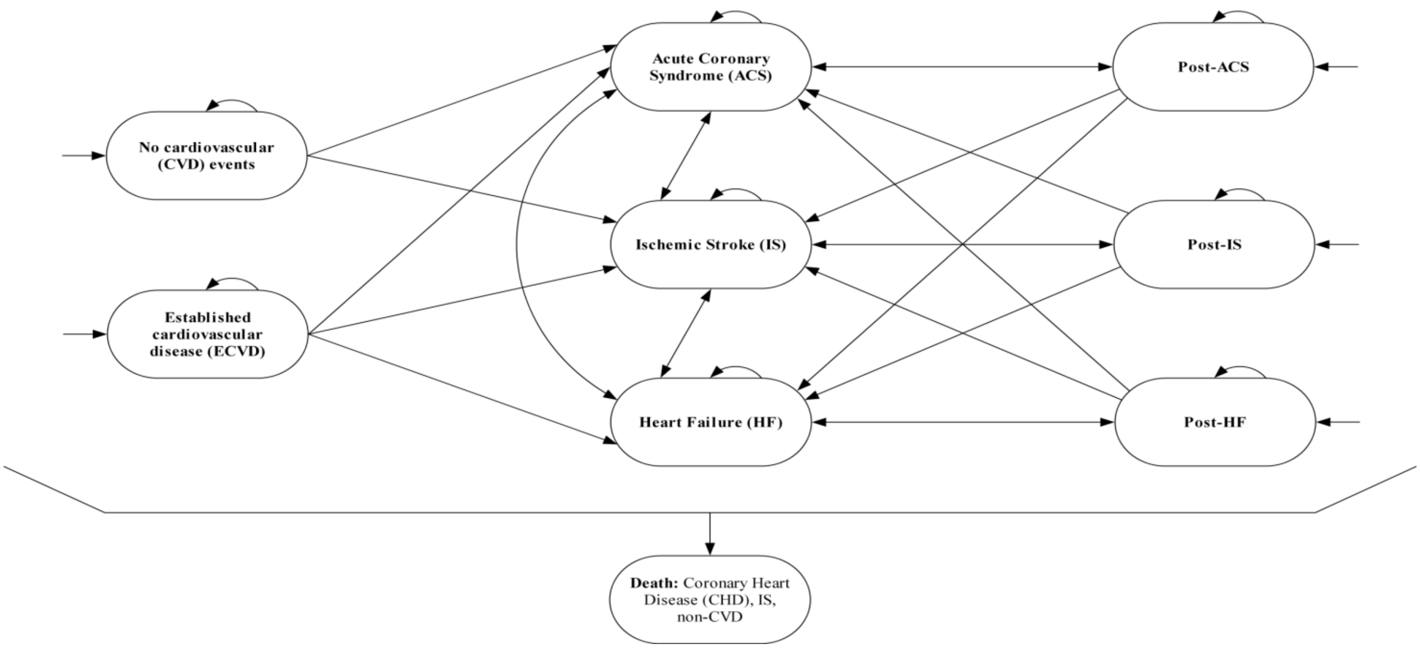
[b] €1= CAD$ 1.4721 (Bank of Canada historical closing rate, June 30, 2016). (www.bankofcanada.ca/rates/exchange/legacy-noon-and-closing-rates/).

Appendix 5: Reviewer Worksheets

Manufacturer's Model Structure

The economic analysis used a cohort state transition model. Patients enter the model in the established cardiovascular disease (CVD) or the post-cardiovascular (CV) health states (i.e., post-acute coronary syndrome [ACS], post-ischemic stroke [IS], or post-heart failure [HF]); the distribution of patients in each of these initial health states is informed by the trial cohort (LAPLACE-2 in the manufacturer's reference case). Patients may then either remain in the initial health state or experience a new CV event, each represented by health states of ACS (also referred as unstable angina or myocardial infarction), IS, and HF (Figure 1). Afterward, they transition to post-CV health states or die (shown in Figure 1 as Post-ACS, Post-IS, Post-HF, CV Death [i.e., coronary heart disease and stroke], and Non-CV Death). Once patients progress from the established CVD state, they cannot return to it. The model captures multiple combined post-CVD health states to track patients' disease histories, allowing for multiple CV events to occur. "No CVD" is a health state in the model, but it is not used for the resubmission.

Figure 1: Health States in the Manufacturer Model



Source: Manufacturer's pharmacoeconomic submission.[1]

Transition probabilities for developing an acute CV event and experiencing CV death were based on the Clinical Practice Research Database (CPRD), a retrospective observational cohort study in multiple UK cohorts. Baseline event rates were also modified by the initial low-density lipoprotein cholesterol (LDL-C) in the population of interest (LAPLACE-2 in the manufacturer reference case). Non-CV mortality was assumed to be the same as in the Canadian general population. The effect of treatment effectiveness on CV risk (ACS, IS, and HF) was based on the absolute LDL-C reduction from the evolocumab phase III clinical trials (LAPLACE-2). The CV event relative risk (RR) per mmol/L of LDL-C reduction was estimated assuming that the relationship between LDL-C reduction and CV events is the same as with statins, an assumption informed by Baigent et al.'s meta-analyses.

Table 12: Data Sources

Data Input	Description of Data Source	Comment
Efficacy	Based on a surrogate outcome of change in LDL-C from the evolocumab phase III clinical trials (LAPLACE-2). CV risk was estimated using the relationship of LDL-C reduction and CV risk from statins based on meta-analysis (Baigent et al.).[7]	Inappropriate. Assuming the same relationship between LDL-C and CV events is not justified; other agents that lower LDL have not had the same relationship to CV events. Furthermore, the RCT of evolocumab using clinically relevant outcomes has been conducted (FOURIER) and indicates that this relationship is not same as for statins.
Natural history	The baseline CV risks were based on the CPRD, a retrospective observational cohort study to estimate event rates in multiple cohorts in the UK. Baseline event rates were also modified by the difference in initial LDL-C between the population of interest and the CPRD population.[1]	Unclear. It is not known how the CV risk in the population compares with that of eligible Canadians or even the trial population. If the risk is greater, the absolute benefit of evolocumab could be overestimated. The baseline risk of outcomes over time was not compared or validated with a treatment-eligible Canadian population. No model validation on this was conducted.
Utilities	Utility data for each CV health state were obtained from a UK study, as the manufacturer claimed that available Canadian data did not provide information for all health states considered in the model or provided disparate utility values based on different instruments.[10]	Appropriate, but might not be applicable to Canadians
Resource use	See costs section.	
Adverse events (indicate which specific adverse events were considered in the model)	Findings from phase III trials (LAPLACE-2, OSLER and GLAGOV) indicated that evolocumab was well tolerated. Therefore, AEs were not modelled.[8,9]	Appropriate. However, uncertainty exists with respect to the true AE rate given limited experience with evolocumab.
Mortality	Details on baseline mortality rates were not provided in the resubmission. In the manufacturer's response, non-CV mortality was assumed to be the same as among the Canadian population (Life Tables).{2} CV death was estimated from the CV events in CPRD and CTTC.[1,7]	Uncertain. The CV death rate might not be applicable to Canadians. If it is greater than observed in an eligible Canadian population, the absolute benefit of evolocumab may be overestimated. No model validation was conducted, leading to uncertainty if a 40-year time horizon (with average starting age of 60 to 63) simulates survival in a treatment-eligible population
Costs		
Drug	Medication costs were obtained from the Ontario Drug Benefit Formulary and the manufacturer. The least expensive alternative within each statin intensity category was chosen.[19]	Appropriate
Administration	Not modelled	Appropriate, assuming self-injected
Event	See natural history	

Data Input	Description of Data Source	Comment
Adverse events	Not modelled	Appropriate
Health state	CV event costs were estimated from published Canadian literature (Goeree, Mittmann, Blackhouse, and Smolderen).[11-14]	Appropriate

AE = adverse event; CPRD = Clinical Practice Research Database; CTTC = Cholesterol Treatment Trialists' Collaboration; CV = cardiovascular; LDL-C = low-density lipoprotein cholesterol; RCT = randomized controlled trial.

Table 13: Manufacturer's Key Assumptions

Assumption	Comment
Natural History and Efficacy	
Observed LDL-C reduction can be used to predict CV risk using data from statin trials and to infer relative efficacy of evolocumab.	Inappropriate. When higher-quality data (clinically important outcomes from RCTs) are available, lower-quality evidence that models surrogate outcomes to clinical outcomes (with inherent assumptions that are uncertain) should not be used. Observed RRs from FOURIER were used in the CDR reference case, although this was challenging, as the manufacturer model was not designed in this manner.
Transition probabilities of CV events were obtained from cohorts from the UK. Baseline event rates were also modified by the difference in initial LDL-C between the population of interest and the CPRD population. Validation of the baseline event rate was not conducted.	Not appropriate. It is not clear that these data reflect the Canadian or even FOURIER trial population CV risk. Best practices of economic evaluation state that model validation should be conducted; while RR reduction was validated, no data were provided to confirm that the baseline risk in this population is similar to that of a treated Canadian population. This may impact absolute benefit.
The efficacy of evolocumab in reducing LDL-C observed in the LAPLACE-2 trial was assumed to be maintained for the duration of treatment (40 years).	Uncertain. No long-term evidence is available. If relative efficacy attenuates over time, the ICUR will be higher. Note that this limitation also applies to observed clinical events from FOURIER (not used in manufacturer reference case).
Combined health states were allowed in the model, assuming the highest cost and the highest transition probability of combined events health states.	Appropriate.
Full compliance with evolocumab over a lifetime horizon is assumed.	Uncertain. There is no evidence to support full compliance; furthermore, it is unclear that evolocumab would be used for decades as modelled.

CDR = CADTH Common Drug Review; CV = cardiovascular; CPRD = Clinical Practice Research Database; ICUR = incremental cost-utility ratio; LDL-C = low-density lipoprotein cholesterol; RCT = randomized controlled trial.; RR = relative risk.

Additional CADTH Common Drug Review Reanalyses

The primary CADTH Common Drug Review (CDR) reanalyses are presented in the main body of the report. Background information on utilities, the FOURIER patient population, and RRs are provided below.

Utility scores: The manufacturer's model used utility scores from a UK study for each health state. CDR reanalyses tested the upper and lower confidence interval (CI), examined a Canadian study (Saw et al.), and reported the 95% CI (Table 14).

Table 14: Range of Quality of Life Tested in the CADTH Common Drug Review Reanalyses

	Matza et al. (2015)[10]				Saw et al. (2016)[16]		
Acute	**Mean**	**SD**	**Lower CI[a]**	**Upper CI**	**Mean**	**Lower CI**	**Upper CI**
Stroke	0.33	0.46	0.27	0.39	0.30	0.20	0.40
ACS	0.67	0.34	0.62	0.72	0.87	0.67	1.00
HF	0.60	0.38	0.55	0.65	0.63	0.61	0.65
Long-term							
Stroke	0.52	0.38	0.47	0.57	0.40	0.27	0.53
ACS	0.82	0.17	0.80	0.84	0.94	0.62	1.00
HF	0.57	0.32	0.53	0.61	0.63	0.61	0.65

ACS = acute coronary syndrome; CI = confidence interval; HF = heart failure; QoL = quality 0f life; SD = standard deviation.

[a] CI calculated based on the study sample size of 200.

Population: A different trial population was also considered in the economic reanalyses. The patient population from LAPLACE-2 was used in the manufacturer's reference case; however, the GLAGOV population was another option in the model.[3,9] After considering the patient characteristics from FOURIER, the patients' lipid measures were more similar to those of the patients in GLAGOV than those of the patients in LAPLACE-2. As a result, the GLAGOV population was used in the CDR reference case. While it would be ideal to select the patient population based on its similarity to the patient population treated in Canada, no information was provided to determine this similarity; as such, a study population that was based on the FOURIER trial (which reported on clinically important outcomes) was used.[15] Baseline event rates from the CPRD were modified by the difference of initial LDL-C between the trial population and the CPRD population; using a population with a lower LDL-C (GLAGOV) may reflect a patient population that is intensively treated with LDL-C lowering therapies.

Table 15 summarizes the patient characteristics from the three trials.

Table 15: Summary of Trial Populations

	LAPLACE-2 Placebo (n = 558)	GLAGOV Cohort (n = 968)	FOURIER Placebo (n = 13,780)
Patients	Patients with primary hypercholesterolemia and mixed dyslipidemia in 198 cities in 17 countries	Patients undergoing a clinically indicated coronary angiogram with angiographic evidence of coronary atheroma after 78 weeks of treatment	Patients with atherosclerotic cardiovascular disease and LDL cholesterol levels of 70 mg per deciliter (1.8 mml/L)
Age, mean (SD), y	59.9 (10.2)	59.8 (9.2)	62.5 (8.9)
Male, no. (%)	291 (52.2)	698 (72.1)	10,398 (75.5)
White race, no. (%)	531 (95.1)	908 (93.8)	11,710 (85.0)
Diabetes, no. (%)	74 (13.3)	199 (20.6)	5,027 (36.5)
LDL-C	107.7 (40.2)	92.6 (27.2)	92 (80 to 109)
Total cholesterol	187.9 (44.3)	166.2 (34.1)	168 (151 to 189)
HDL cholesterol	54.5 (16.5)	46 (12.8)	44 (37 to 53)
Triglycerides	114 (85 to 154)	120 (89 to 166)	133 (99 to 181)
Lipoprotein (a)	34 (12 to 149)	32 (12 to 152)	37 (13 to 164)

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

Table 16 also shows the distribution of initial health states in the economic model for the LAPLACE-2 and GLAGOV populations.

Table 16: Distribution of Initial Health States in the Model

	LAPLACE-2[3]	GLAGOV[9]
Initial ECVD	0.4543	0.6130
Initial ACS	0	0
Initial post-ACS	0.2696	0.3622
Initial IS	0	0
Initial post-IS	0.0587	0.0155
Initial HF	0	0
Initial post-HF	0.0913	0
Initial post-ACS + post-IS	0.0087	0.0093
Initial post-ACS + post-HF	0.1065	0
Initial post-IS + post-HF	0.0087	0
Initial post-ACS + post-IS + post-HF	0.0022	0

ACS = acute coronary syndrome; ECVD = established cardiovascular disease; HF = heart failure; IS = ischemic stroke.

Relative efficacy: The manufacturer's model was challenging to modify, as findings from the FOURIER study could not be directly used. In the manufacturer's model, the RR of evolocumab for each CV event was calculated based on RR per mmol/L LDL-C reduction and the absolute LDL reduction from evolocumab:

Total RR = RR per mmol/L to the power of absolute LDL reduction from evolocumab

For example: RR ACS = 0.73 ^ 1.6328 = 0.5982

An absolute LDL reduction of 1.6328 mmol/L was used in the model for the evolocumab + SOC group using the GLAGOV population.

In order for the observed hazard ratio (HR) from the evolocumab + SOC group from FOURIER to be used in the economic model, the hazard ratio was converted to RR per mmol/L LDL-C reduction by taking the inverse power of the absolute LDL reduction (1/1.6328). Table 17 shows the converted RR used in the economic model.

Table 17: FOURIER Relative Risks

	Observed HR From FOURIER[15]			Converted RR per mmol/L			
	Mean	Lower CI	Upper CI	Mean	Lower CI	Upper CI	Original Model Values
CHD death	1.05	0.88	1.25	1	1	1	0.8 (0.76 to 0.85)
CHD and IS death in SA using primary end point	0.85	0.79	0.92	0.9053	0.8656	0.9502	0.8 (0.76 to 0.85)
ACS	0.73	0.65	0.82	0.82	0.77	0.89	0.71 (0.58 to 0.87)
IS	0.75	0.62	0.92	0.84	0.75	0.95	0.69 (0.50 to 0.95)
HF	NA			NA			0.71 (0.58 to 0.87)

ACS = acute coronary syndrome; CHD = coronary heart disease; CI = confidence interval; HF = heart failure; HR = hazard ratio; IS = ischemic stroke; RR = relative risk; SA = sensitivity analysis; SD = standard deviation.

The observed hazard ratio on coronary heart disease (CHD) death was not significant in FOURIER; thus, the RR of CHD death was set to 1 in the CDR reanalyses. In the manufacturer's reference case, the LDL-C lowering effect on HF was not included (RR HF = 1); it was also assumed in the CDR reference case that HF was not an observed outcome. However, it was tested in the sensitivity analysis (SA) below (Table 20) to assess the possible LDL-C-lowering effect on HF (assuming RR HF = RR ACS).

It is acknowledged that the CDR reanalysis incorporating FOURIER study findings may not be accurate given the parameter manipulation required. As noted above, if the manufacturer submission adhered to best practices for economic evaluation, the model should be designed to directly use FOURIER trial results.

Additional CDR reanalyses: An additional SA was conducted in which a new reference case used FOURIER RR data and characteristics (LDL-C) from LAPLACE-2 were assumed.[3,15] While it may be more appropriate to use the GLAGOV patient population (given the limited information and validation information provided), there is uncertainty on what best reflects the Canadian treatment-eligible population. However, all ICURs remain above $250,000 per QALY, as shown in Table 20.

Furthermore, while a mortality benefit was not observed in FOURIER, given that it was an event-driven study, it is possible that survival may occur (see clinical report). Sensitivity analysis on the CDR reference case was conducted assuming the RR of mortality due to CHD death alone. CHD and IS death were identical to the RR of the primary outcome of FOURIER (0.85, or 0.9053 per mmol/L; see Table 17). Another estimate of 0.86 per mmol/L from the Cholesterol Treatment Trialists' Collaboration (CTTC) 2010 suggested in the manufacturer's response was also tested in the sensitivity analysis (see Table 20).

The following tables show the event rates from the CDR reference case using the converted RRs with the GLAGOV population and the event rates from the manufacturer's reference case.

Table 18: Event Rates in the Manufacturer's Reference Case

	Evolocumab + SOC	SOC	Ezetimibe + SOC
Total Predicted Event Rates, LAPLACE-2 Population (40 Years)			
CVD events	1.16	1.65	1.49
ACS	0.35	0.71	0.59
IS	0.06	0.12	0.10
HF	0.32	0.28	0.29
CHD death	0.31	0.43	0.40
Stroke death	0.11	0.10	0.10
Non-CVD mortality	0.56	0.46	0.49

ACS = acute coronary syndrome; CDR = CADTH Common Drug Review; CHD = coronary heart disease; CVD = cardiovascular disease; HF = heart failure; IS = ischemic stroke; RR = relative risk; SOC = standard of care.

Note: RRs for ezetimibe + SOC were based on the converted FOURIER RRs and the LDL-C reduction from LAPLACE-2.[3,15]

Table 19: Event Rates in the CADTH Common Drug Review Reference Case

	Evolocumab + SOC	SOC	Ezetimibe + SOC
Total Predicted Event Rates, GLAGOV Population (40 Years)			
CVD events	1.14	1.36	1.27
ACS	0.45	0.64	0.57
IS	0.08	0.1	0.09
HF	0.18	0.18	0.18
CHD death	0.35	0.36	0.35
Stroke death	0.09	0.09	0.09
Non-CVD mortality	0.54	0.53	0.53

ACS = acute coronary syndrome; CDR = CADTH Common Drug Review; CHD = coronary heart disease; CVD = cardiovascular disease; HF = heart failure; IS = ischemic stroke; RR = relative risk; SOC = standard of care.

Note: RRs for ezetimibe + SOC were based on the converted FOURIER RRs and the LDL-C reduction from LAPLACE-2.[3,15]

Table 20: Additional CADTH Common Drug Review Reanalyses

	Description	Evolocumab + SOC Versus SOC			Evolocumab + SOC Versus Ezetimibe + SOC		
		Incremental Cost ($)	Incremental QALYs	ICUR ($/QALY)	Incremental Cost ($)	Incremental QALYs	ICUR ($/QALY)
	Manufacturer's base case	115,055	1.03	112,196	113,648	0.72	158,855
3	**Observed RR From FOURIER and LAPLACE-2 Population (ACS and IS)**						
3a	Excludes LDL-C lowering effect on HF	102,832	0.13	792,576	102,256	0.09	1,134,553
3b	Includes LDL-C lowering effect on HF	102,185	0.23	447,366	101,966	0.16	639,411
4	**Plausible Reference Case (Observed RR From FOURIER and GLAGOV Populations)**						
4a	Excludes LDL-C lowering effect on HF	**122,841**	**0.12**	**1,007,961**	**121,737**	**0.08**	**1,478,417**
4b	Includes LDL-C lowering effect on HF	122,274	0.22	564,762	121,488	0.15	827,262
4c	RR on CHD and IS death from FOURIER primary end point (0.9053 per mmol/L)	127,677	0.46	278,021	126,048	0.32	396,520
4d	RR per mmol/L reduction based on CTTC estimates (0.86 on CHD and IS death)	130,000	0.62	209,294	128,105	0.43	299,133

ACS = acute coronary syndrome; CHD = coronary heart disease; CTTC = Cholesterol Treatment Trialists' Collaboration; HF = heart failure; ICUR = incremental cost-utility ratio; IS = ischemic stroke; LDL-C = low-density lipoprotein cholesterol; QALY = quality-adjusted life-year; RR = relative risk; SOC = standard of care; vs. = versus.

References

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