CADTH

CADTH Reimbursement Review

CADTH Reimbursement Recommendation

(Draft)

Inclisiran (Leqvio)

Indication: as an adjunct to lifestyle changes, including diet, to further reduce low-density lipoprotein cholesterol (LDL-C) level in adults with Non-familial hypercholesterolemia with atherosclerotic cardiovascular disease who are on maximally tolerated dose of a statin, with or without other LDL-C -lowering therapies

Sponsor: Novartis Pharmaceuticals Canada Inc.

Recommendation: Do Not Reimburse

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Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that inclisiran not be reimbursed as an adjunct to lifestyle changes, including diet, to further reduce low-density lipoprotein cholesterol (LDL-C) level in adults with Non-familial hypercholesterolemia (nFH) with atherosclerotic cardiovascular disease (ASCVD) who are on maximally tolerated dose of a statin, with or without other LDL-C -lowering therapies.

Rationale for the Recommendation

As outlined in the 2022 CDEC final recommendation for inclisiran, there were two phase III, double-blind randomized controlled trials (RCTs) (ORION-10, N=1561 and ORION-11, N=1617) that demonstrated that there was a statistically significant improvement compared with placebo in lowering LDL-C levels in adult patients with nFH with ASCVD who were receiving a maximally tolerated dose of a statin or who were statin intolerant, the between-group differences in percentage change in LDL-C from baseline to day 510 were –57.64 (95% CI, -60.86 to -54.43) in ORION-10 and -53.5 (95% CI: -56.66 to -50.35) in ORION-11 (all P<0.0001). However, clinically relevant cardiovascular-related morbidity and mortality outcomes were exploratory, and the trial was not powered to detect statistical significance for these outcomes. Additionally, it was noted that the long-term efficacy and safety of inclisiran require further review, and two ongoing studies (ORION-4 and ORION-8) were expected to provide further evidence regarding the efficacy and safety of inclisiran in preventing pertinent clinical outcomes. As part of the evidence base for the resubmission, CDEC considered a post hoc pooled analysis of major adverse cardiovascular events (MACE) from the ORION-10 and ORION-11 trials, as well as the ORION-3 and ORION-8 studies, both long-term open-label extensions, as well as a pooled analysis of safety data from seven different ORION trials. A key limitation to the pooled analysis of MACE was that it was conducted post hoc and included exploratory outcomes, as noted above. These limitations precluded CDEC from determining whether inclisiran reduces the risk of cardiovascular morbidity and mortality. The open-label extensions, ORION-3 and ORION-8, each lacked a comparator group, and this also precluded CDEC from drawing any conclusions about the relative longer-term efficacy and safety of inclisiran versus placebo for these outcomes.

Patient input received for this review emphasized the need for an additional, less burdensome, treatment that would lower LDL-C levels, decrease the risk of cardiovascular morbidity and mortality, have fewer side effects than existing treatments, and improve health related quality of life. The ORION studies have demonstrated that inclisiran reduces LDL-C levels compared to placebo in patients with ASCVD. However, there is insufficient evidence to assess the clinical benefit of inclisiran in terms of reducing the risk of cardiovascular events, cardiovascular death, or all-cause mortalityWhile CDEC recognized that the bi-annual dosing regimen may provide patients with a more manageable administration schedule, no health-related quality of life (HRQoL) data was included, and therefore the impact of inclisiran on HRQoL is unknown.

Discussion Points

- CDEC discussed that the post hoc pooled analysis of MACE from ORION-10 and ORION-11 has significant methodological limitations. ORION-3 and ORION-8 lack a control group. CDEC noted that the main issues with the post hoc pooled analysis of major adverse cardiac events (MACE) from the ORION-9, -10, and -11 trials that the sponsor submitted is that MACE and its components were only an exploratory outcome from these ORION trials, and it was a post hoc analysis. The fact that MACE and its components were exploratory outcomes from these ORION trials also introduces the potential for bias. Sample sizes were not determined based on these outcomes, events were captured via the safety population, and definitions may not have been inclusive or specific enough; there was no blinded, centralized assessment of events, and the timing was likely insufficient to assess cardiovascular events. In addition, using a post hoc analysis introduces significant potential for bias, as an investigator may be biased by their ability to see the data when deciding what analyses to conduct and how to construct the composite outcome. Finally, combining results from all three ORION trials is inappropriate, as this ignores the fact that these trials feature two distinct populations, each separately identified within the indication. Additionally, there could have been issues with pooling ORION-10 and -11, as there are some differences in baseline characteristics between these two study populations, most notably that all patients in ORION-10 had ASCVD, while approximately 88% of patients in ORION-11 had ASCVD, with the remaining categorized as ASCVD-RE. There was also a higher percentage of patients who discontinued treatment in ORION-10 compared to ORION-11, further reinforcing that these are two distinct study populations. As a result, the ability to draw a conclusion of the effect of inclisiran on cardiovascular morbidity or mortality is limited.
- While CDEC recognized that that there is a health need for patients who do not reach LDL-C targets despite available treatments and that reducing LDL-C levels is an important outcome in patients with ASCVD, it was noted that while for many treatments there is evidence that lowering LDL-C levels correlates with a reduction in risk of cardiovascular events, extrapolation from other trials or to other populations based on LDL-C levels is not substantiated by current evidence.
- CDEC discussed that the ORION-4 study, which was noted in the recommendation issued in 2022 as a potential source of data for cardiovascular morbidity and mortality, features a population with ASCVD and that it would provide further evidence to better characterize the efficacy and safety of inclisiran in preventing pertinent clinical outcomes, including the reduction of cardiovascular events, cardiovascular-related death, and all-cause mortality, and hence contribute valuable information regarding the long-term safety and efficacy of inclisiran, however, ORION-4 study is still ongoing and was not submitted by the sponsor.
- In the recommendation issued for inclisiran in 2022, CDEC discussed that there is no evidence that inclisiran will be better tolerated in patients who did not respond or were intolerant to PCSK9 inhibitors and that the efficacy of switching from PCSK9 inhibitors to inclisiran on reduction in LDL-C levels and cardiovascular morbidity and mortality is unknown. CDEC discussed that there is no new evidence submitted by the sponsor that changes this.
- Given that hypercholesterolemia requires lifelong treatment, CDEC noted at the time of the recommendation that was issued in 2022 that there is uncertainty regarding the long-term efficacy and safety of inclisiran for the treatment of adult patients with nFH with ASCVD. CDEC also noted that the novel mechanism of action for inclisiran adds to the uncertainty. The ORION-3 (4-year open label extension of the phase 2 ORION-1 trial) and ORION-8 (3-year open label extension of the ORION-3 trial as well as ORION-9, ORION-10 and ORION-11) long term extension trials provided some evidence that the reductions in LDL-C seen in the ORION trials is durable and there was no evidence of new safety issues, however any conclusions that can be drawn from these trials are limited by the lack of MACE outcomes, lack of comparator group, and lack of blinding.
- In the recommendation issued for inclisiran in 2022, CDEC discussed the lack of direct comparative evidence for inclisiran versus the PCSK9 inhibitors or other add-on agents such as ezetimibe. They noted that one sponsor-submitted indirect treatment comparison (ITC) suggested that inclisiran does not have a consistent nor distinct difference in efficacy in LDL-C reduction compared with evolocumab or alirocumab, although they also noted uncertainty about the ITC results due to the inherent heterogeneity across trials in the networks, and the fact that the duration of follow-up (24 weeks) was short given the chronic nature of the condition. No additional ITCs were provided for the resubmission.

Background

In Canada, cardiovascular disease (CVD) is the second leading cause of death and accounted for almost 20% of all deaths in 2020. Despite its pathophysiological complexity, the one pre-requisite for atherosclerotic plaque development is the presence of low density lipoprotein cholesterol (LDL-C). Hypercholesterolemia can be grouped into two forms: non-familial hypercholesterolemia (nFH) and familial hypercholesterolemia (FH, also referred to as acquired or genetic hypercholesterolemia). Non-familial hypercholesterolemia is characterized by elevated LDL-C levels. Its etiology is likely due to a complex interplay between several genetic, environmental risk factors that increase the risk of nFH including diet, smoking, physical inactivity, and other factors known to be associated with an increased risk of CVD (e.g., diabetes, chronic kidney disease, and hypertension). In Canada, the one year incidence rate for atherosclerotic cardiovascular disease (ASCVD) ranges between 7.2- 8.8 per 1000 person years, and the 5 year prevalence of ASCVD ranges between 6.91%- 8.55% in adults.

Elevated LDL-C is directly associated with the development of atherosclerosis and ASCVD. The three main subcategories of ASCVD are coronary artery disease (CAD), cerebrovascular disease, and peripheral arterial disease (PAD). Individuals with hypercholesterolemia and a history of an atherosclerotic event are categorized as having established clinical ASCVD (i.e., they are secondary prevention patients), while individuals with hypercholesterolemia at risk of developing ASCVD are considered as primary prevention patients. A subset of primary prevention patients at greater risk of ASCVD are referred to as having an ASCVD risk-equivalent (ASCVD-RE). Patient with ASCVD-RE are defined as those with type 2 diabetes mellitus, FH, or with a 10-year risk of a CV event of ≥20% as assessed by the Framingham Risk Score (FRS) for CVD or equivalent. The proportion of the overall ASCVD population who are considered to be at high-risk is estimated to be approximately 25%. Following Canadian guidelines, published literature, and validation with Canadian clinicians, these high-risk nFH ASCVD patients are defined as patients with any of the following criteria: a) diabetes, b) recurrent vascular events, c) peripheral arterial disease (PAD) or d) acute coronary syndrome (ACS) in the past 12 months; and with LDL-C levels >1.8 mmol/L despite maximally tolerated dose (MTD) statins with or without other lipid lowering therapies (LLTs). Throughout this document, the high-risk ASCVD subgroup will refer to patients with any of these criteria.

FH is one of the most common genetic disorders and is caused by mutations in the genes encoding LDL receptor (LDLR), apolipoprotein B (Apo-B), or proprotein convertase subtilisin/kexin type 9 (PCSK9), leading to high plasma levels of LDL-C. Depending on the number of mutant alleles, patients can be categorized as having homozygous FH (HoFH) or heterozygous FH (HeFH). HeFH has an estimated prevalence of approximately 1 in 250 to 1 in 311 individuals. The clinical presentation of FH is variable, affected by the number and type of mutations together with other genetic factors. Individuals with FH have elevated LDL-C levels from a young age, and the ongoing exposure to elevated LDL-C results in a higher cumulative risk of developing ASCVD. Patients with FH may present with physical findings such as tendon xanthomata or xanthelasma. FH is associated with an increased risk of CV events compared with the general population.

Inclisiran has a Health Canada indication as an adjunct to lifestyle changes, including diet, to further reduce low-density lipoprotein cholesterol (LDL-C) level in adults with the following conditions who are on maximally tolerated dose of a statin, with or without other LDL-C -lowering therapies:

- Heterozygous familial hypercholesterolemia (HeFH), or
- Non-familial hypercholesterolemia with atherosclerotic cardiovascular disease.

Inclisiran is a double-stranded small interfering RNA that causes the degradation of PCSK9 mRNA. It is available as a subcutaneous injection through a single-dose pre-filled syringe. The Health Canada–approved dose for this indication is 284 mg administered as a single subcutaneous injection initially and again at 3 months followed by every 6 months.

Submission History

Inclisiran was previously reviewed by CADTH in February 2022 for the same indication, and the recommendation was to not reimburse. Key reasons for this recommendation included the fact that there was insufficient evidence inclisiran reduced cardiovascular morbidity and mortality, or all-cause mortality, as the pivotal trials, ORION 9, 10 and 11, were not designed to assess these outcomes. Additionally, CDEC noted that the long term efficacy and safety of inclisiran has not been determined, and that there were two ongoing studies, ORION-4 and ORION-8 that are expected to provide further evidence to better characterize the pertinent clinical outcomes as well as provide long term efficacy and safety data. CDEC also noted that there was no direct comparison of inclisiran to evolocumab or alirocumab, or other add-on agents, and that there were limitations with the submitted indirect treatment comparison (ITC), including the relatively short follow-up (24 weeks) in a chronic condition.

The sponsor outlined the basis for their resubmission. In an effort to address the lack of evidence for reduction of CV morbidity/mortality and all-cause mortality, the sponsor included a post hoc pooled analysis of major adverse cardiovascular events (MACE) in the pivotal ORION studies, and to address concerns over long term efficacy and harms, the findings of the long-term extensions, ORION-3 and ORION-8. To address the issue over lack of long-term safety data, in addition to ORION-3 and -8, the sponsor submitted a pooled analysis of 7 ORION trials. Finally, the sponsor submitted a revised budget impact model to address CADTH's concerns in the first recommendation.

Sources of Information Used by the Committee

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

- a review of 2 RCTs in adult patients with nFH with ASCVD
- a review of post hoc pooled analysis of major adverse cardiovascular events (MACE) in the pivotal ORION studies
- a review of 2 long-term extension studies (ORION-3 and ORION-8)
- patients' perspectives gathered by patient groups, the Canadian Heart Patient Alliance (CHPA) and the HeartLife Foundation
- input from public drug plans that participate in the CADTH review process
- Three of clinical specialists with expertise diagnosing and treating patients with HeFH and nFH with ASCVD
- input from 13 clinician groups, including Alberta Cardiovascular Disease Prevention Collaborative, BC Lipid specialists, CHU Dr-Georges-L-Dumont, Cambridge Cardiac Rehab Program, Canadian Cardiovascular Society (CCS) Dyslipidemia Guideline Committee, Cardiology Association of Niagara, Egyptian Cardiologists of Niagara, Kawartha Cardiology Clinic, Lipid Clinic of McMaster University and Hamilton Health Sciences, Mazankowski Alberta Heart Institute, Oakville Cardiologists, Service of cardiology, Internal Medicine Department and Heart failure group St. Thomas Elgin General Hospital, and Western University, Division of Cardiology, Cardiac Rehabilitation and Secondary Prevention Program
- a review of the pharmacoeconomic model and report submitted by the sponsor

Stakeholder Perspectives

Patient Input

Two patient groups, the Canadian Heart Patient Alliance (CHPA) and the HeartLife Foundation provided input via survey and interviews (CHPA) and by executives of the HeartLife Foundation.

Patients describe a condition that is very difficult to manage, impacts their physical and mental well-being, and has a significant financial burden on families and impacts their quality of life. Symptoms like shortness of breath, chest pain and fatigue were stated by the respondents who indicated the negative impact of a heart attack, bypass surgery or stroke on themselves and their families. Many with a family history of heart disease and/or high cholesterol commented on their fear of following a family pattern of early death.

Adherence and access to newer treatment such as the PCSK9 inhibitors were identified by patients as key challenges in managing their condition. Patients emphasized the importance of having a safe, tolerable and effective treatment to maintain their LDL-C below recommended thresholds. Patients also noted the importance of having a less frequent dosing regimen in managing their condition.

The patient groups stated that patients seek a safe, tolerable and effective treatment that can minimize the long-term health consequences by effectively managing LDL-C levels below the recommended threshold. Patients also want an accessible therapy with a more affordable and manageable treatment regimen, less frequent dosing, fewer side effects, easier administration, and less disruption to work or daily life.

Clinician Input

Input From Clinical Experts Consulted by CADTH

Non-adherence, intolerance to high intensity statins, inability to reach recommended lipid targets despite MTD of statin and ezetimibe, and lack of access to PCSK9 inhibitors are the major unmet needs identified by the clinical experts in treatment of patients with HeFH and with nFH with ASCVD. Accordingly, the clinical experts believed that in addition to being another PCSK9-targeting drug, inclisiran may help with non-adherence due to the less frequent dosing schedule.

The clinical experts believed that for patients with HeFH, in addition to those patients unable to reach LDL-C target despite maximally tolerated statin, with or without ezetimibe, patients who would be especially well-suited would include patients with other risk factors such as smoking, diabetes, hypertension, or elevated Lp(a). For patients with nFH with ASCVD the clinical experts believed that well-suited patients would include those unable to tolerate high intensity statins, those with early disease onset or recurrent disease, those whose LDL-C is far from threshold, and those with the risk factors identified for patients with HeFH. The clinical experts also referenced the 2021 CCS guidelines, which identified which secondary prevention patients are likely derive the most benefit from intensification of statin therapy with the additional use of a PCSK9 inhibitor. These included patients with recent ACS (within 52 weeks), diabetes mellitus or metabolic syndrome, polyvascular disease, symptomatic PAD, recurrent MI, MI in the past 2 years, previous CABG, LDL-C of 2.6 mmol/L or greater or HeFH, or Lp(a) of 120 nmol/L or greater.

The clinical experts noted that genetic testing should not be required to confirm diagnosis of HeFH due to lack of availability of testing, and they also noted that HeFH is underdiagnosed in Canada. Various lipid parameters would be used to assess response to treatment in addition to LDL-C, including non-high density lipoprotein cholesterol (HDL-C) and ApoB. Although there is no recent guidance on how frequently to assess response, after the initial titration response is typically assessed every 6 to 12 months.

Clinician Group Input

There were 13 clinician groups provided input: Alberta Cardiovascular Disease Prevention Collaborative (8 clinicians contributed to the input), BC Lipid specialists (11 clinicians contributed to the input), CHU Dr-Georges-L-Dumont (CHUDGLD; 6 clinicians contributed to the input), Cambridge Cardiac Rehab Program (6 clinicians contributed to the input), Canadian Cardiovascular Society (CCS) Dyslipidemia Guideline Committee (14 clinicians contributed to the input), Cardiology Association of Niagara (3 clinicians contributed to the input), Egyptian Cardiologists of Niagara (3 clinicians contributed to the input), Kawartha Cardiology Clinic (7 clinicians contributed to the input), Lipid Clinic of McMaster University and Hamilton Health Sciences (1 clinician contributed to the input), Mazankowski Alberta Heart Institute (3 clinicians contributed to the input), Oakville Cardiologists (9 clinicians contributed to the input), Service of cardiology, Internal Medicine Department and Heart failure group St. Thomas Elgin General Hospital (STEGH; 5 clinicians contributed to the input), and Western University, Division of Cardiology, Cardiac Rehabilitation and Secondary Prevention Program (3 clinicians contributed to the input).

The clinician groups agreed that the major issues with managing hypercholesterolemia, whether it be in HeFH or nFH patients with ASCVD, are adherence (as well as intolerance) and lack of accessibility of drug therapies, and that the main outcomes of interest are reduction in lipid parameters (LDL-C, non-HDL-C and ApoB) at 6 months initially and then assessed annually thereafter.

The clinician groups believed that inclisiran would be best suited for patients at risk of ASCVD or with FH who require additional lipid-lowering therapy, who become refractory to statins and ezetimibe, along with those who struggle with adherence or tolerability.

Drug Program Input

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

- Relevant comparators
- considerations for initiation of therapy
- considerations for discontinuation of therapy

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

Clinical Evidence

Systematic Review

Description of Studies

The major focus of this resubmission was a post hoc pooled analysis of MACE from the ORION-9, -10, and -11 trials. These trials, all included in the original submission, were phase III, double-blind, randomized controlled trials (RCTs) comparing inclisiran to placebo in adult patients with HeFH (ORION-9) or ASCVD (ORION-10 and -11) and ASCVD risk equivalent (ORION-11) [i.e., those with diabetes, FH or a 10-year risk of a CV event of ≥20% as assessed by the Framingham Risk Score for Cardiovascular Disease or equivalent]) who were receiving MTD statins, or who were statin intolerant. Patients in the ORION-9 had a history of HeFH with a diagnosis of HeFH by genetic testing or phenotypic Simon Broome criteria; and/or a documented history of untreated LDL-C of >190 mg/dL, and a family history of FH, elevated cholesterol or early heart disease may indicate FH. In all three ORION studies, patients were randomized 1:1 to either inclisiran sodium 300 mg or placebo in addition to MTD statin. The ORION-9, -10, and -11 trials enrolled 482, 1561, and 1617 patients, respectively. The studies were all 18 months in duration with patients receiving four 300 mg doses of inclisiran sodium on Day 1, Day 90, Day 270, and Day 450. The primary outcome of the ORION-9, -10, and -11 trials was the percent change in LDL-C from baseline to Day 510. In all trials the co-primary endpoint was the average percentage change in LDL-C from baseline over the period after Day 90 and up to Day 540, reflecting the start of the biannual dosing regimen. Incidences of CV death, resuscitated cardiac arrest, non-fatal myocardial infarction (MI), non-fatal stroke (ischemic and hemorrhagic) were exploratory outcomes in the ORION trials within the composite outcome of MACE, and total deaths was a secondary outcomes reported as adverse events (AEs) in the ORION studies.

Baseline characteristics of the ORION trials were balanced between groups, and generally applicable to the Canadian population. The ORION-9 trial enrolled patients with a median age of 56 years and a relatively even ratio of males and females (47.1% male, 52.9% female) with either ASCVD (27.4%) or ASCVD RE (72.6%). A total of 73.9% of patients were on high intensity statins at baseline, with 25.3% either partially or completely intolerant to statins, and 52.3% were treated with ezetimibe. The ORION-10 trial enrolled mostly males (69.4%) with a median age of 67 years, all with ASCVD (91.1% CHD). Approximately two-thirds (69.4%) of patients were on a high intensity statin at baseline, with 22.0% partially or completely intolerant. A total of 9.9% of patients were treated with ezetimibe. ORION-11 enrolled patients with ASCVD (87.4%) and ASCVD RE (12.6%). Patients were mostly males (71.7%) with a median age of 65 years. A total of 78% of patients were receiving high intensity statins, while 11.4% were considered partially or completely intolerant, and 7.1% of patients were treated with ezetimibe.

Efficacy Results in Patients with nFH with ASCVD

MACE

In the ORION-9, -10, and -11 trials, the exploratory endpoint of MACE was defined as the composite of CV death, cardiac arrest, non-fatal MI, and non-fatal stroke (haemorrhagic or non-haemorrhagic) using pre-defined Medical Dictionary for Regulatory Activities (MedDRA) search.

As part of their resubmission, the sponsor conducted a pooled analysis of clinical outcomes from the ORION-9, -10, and -11 trials and they also provided what they referred to as a sensitivity analysis that pooled data from the ORION-10 and -11 studies. The

pooled analysis of all 3 trials is not relevant for this review, as it combines the HeFH and the nFH with ASCVD populations, and these two populations are being viewed separately for this review, consistent with the indication. The sensitivity analysis that was conducted to assess the effects of inclisiran (n=1494) compared to placebo (n=1477) on MACE within the ASCVD and ASCVD-RE populations is relevant.

[redacted]

LDL-C

The co-primary endpoints of percent change in LDL-C from baseline to Day 510 and time-average percent change in LDL-C from baseline after Day 90 and up to Day 510 was the same for the three trials ORION-9, ORION-10, and ORION-11.

The between-group difference between inclisiran and placebo in percent reduction in LDL-C in ORION-10 was - 52.3% (95% CI: -55.7, -48.8), p<0.0001, and in ORION-11 was -49.9% (95% CI: -53.1, -46.6), p<0.0001. For the time-average percent change in LDL-C from baseline after Day 90 and up to Day 510 the LSM difference from placebo favoured inclisiran in ORION-10: −53.78% (95% CI: −56.23, −51.33) and ORION-11: −49.17% (95% CI: −51.57, −46.77); all P < 0.0001). The results of the sensitivity analyses for both outcomes were consistent with the overall population.

Harms Results in Patients with nFH with ASCVD

The frequency of AEs was consistent between inclisiran and placebo treated patients, as well as across trials with patients experiencing at least one AE in 73.5% vs. 74.8%, and 82.7% vs 81.5% in ORION-10, and -11, respectively. In ORION-10 and -11, SAEs occurred in 22.4% and 22.3% of inclisiran treated patients compared to 26.3% and 22.5% of placebo treated patients. The WDAEs in ORION-10 and ORION-11 were similar with 2.4% and 2.8% of inclisiran-treated patients, and 2.2% of placebo-treated patients in each trial withdrawing due to AEs, respectively.

No difference in neurologic events and neurocognitive disorders was observed with inclisiran and placebo in all ORION trials, however, the frequency was higher in all placebo groups. In all trials, fewer placebo treated patients reported AEs at the injection site than those treated with inclisiran. Injection site reactions were mild to moderate, and no severe reactions were seen across trials. There were no clear and consistent differences between inclisiran and placebo for other notable harms of hypersensitivity reactions, renal safety, or hepatic safety.

Critical Appraisal

- There are a number of issues associated with the post hoc pooled analysis provided by the sponsor for this resubmission. First of all, it is a post hoc analysis, which increases the potential for bias. Their primary analysis includes all three pivotal trials (ORION-9 to -11), however this combines two separate populations of patients, patients with HeFH and patients with nFH with ASCVD, and these patients are being considered separately for this review. Importantly, the ORION-9 to -11 trials were not powered to assess MACE, the events were captured via the safety population and the definitions used may not be inclusive or specific enough, and there was no blinded, centralized assessment of events. Otherwise, the ORION-9 to -11 trials appear to have been reasonably well-conducted, with adequate measures to maintain blinding, a multiple testing procedure to reduce risk of type 1 error, and low dropout rates.
- With respect to external validity, key issues are that clinical outcomes such as cardiovascular mortality and morbidity were not assessed in the pivotal ORION trials, and there was no active comparator, such as the PCSK9 inhibitors. Additionally, health-related quality of life (HRQOL) was not assessed in any of the included trials.

Long-Term Extension Studies

ORION-3 and ORION-8

Description of Studies

ORION-3 was a 4-year open-label extension study of the phase 2 ORION-1 trial. The primary objective of this study was to assess the effect of long-term treatment with twice-yearly siRNA therapeutic inclisiran dosing on LDL-C reductions at day 210 compared to baseline in ORION-1. The secondary and exploratory objectives were to assess the effects of inclisiran on cholesterol and other lipids levels and PCSK9 levels up to 4 years in each arm, as well as the long-term safety and tolerability of inclisiran. Another exploratory objective was to evaluate the effects of transitioning from evolocumab to inclisiran. A total of 382 participants were enrolled from 52 centres across 5 countries, among them 56 patients were enrolled from Canadian centres.

ORION-8 is a global open-label, long-term extension study in subjects with ASCVD, ASCVD-RE, or HeFH and elevated LDL-C despite MTD of LDL-C lowering therapies who have completed the phase II ORION-3 study, or any of the phase III ORION-9, ORION-10, or ORION-11 studies. The primary objectives of the study are to evaluate the effect of inclisiran treatment on the proportion of subjects achieving prespecified LDL-C targets, and the safety and tolerability of long-term use of inclisiran. The secondary objectives are to evaluate the effect of inclisiran on LDL-C levels and other lipids and lipoproteins. The study has enrolled 3,274 participants [redacted]

Efficacy Results

Of the original ORION-1 cohort of 497 patients, 290 of 370 patients allocated to drug continued into the inclisiran-only arm and 92 of 127 patients allocated to placebo entered the switching-arm in the ORION-3 extension study conducted between March 24, 2017, and Dec 17, 2021. Overall, efficacy results were consistent and sustained up to the end of the study. In the inclisiran-only arm, LDL-C was reduced by 47.5% (95% CI: 50.7 to 44.3) at day 210 and sustained over 1440 days. During the 4 years of open-label extension, the mean percentage change and mean absolute change in LDL-C concentrations in the inclisiran-only arm ranged between -34.3% to -53.8%, and -1.13 mmol/L to -1.76 mmol/L, respectively, with the upper limit of the 95% CI at all time points being lower than -30% and excluding zero. The mean percentage change and mean absolute change in LDL-C in the switching arm ranged between -38.2% to -65.7%, and -1.20 mmol/L to -2.00 mmol/L, respectively.

In the inclisiran-only arm, the mean percentage change in total cholesterol ranged from -21.1% to -30.2%, remaining relatively consistent throughout the follow-up period. Non-HDL-C, Apo-B, and triglycerides also remained consistently decreased throughout the follow-up period. Lp(a) concentration decreased by -16.3% at day 30 with no meaningful changes thereafter.

[redacted]

[redacted]

Harms Results

The most common AEs in ORION-3 were infection, hypertension, arthralgia and fatigue. In the inclisiran-only arm, 275 (96.8%) patients experienced at least one AE. A total of 104 (36.6%) patients experienced at least one SAE. Nineteen (6.7%) patients and 12 (4.2%) patients discontinued the study treatment due to AE and SAE, respectively.

Overall, of a total of 87 patients in the switching arm, 80 (92%) patients experienced at least one AE. Thirty (34.5%) patients experienced at least one SAE. Five (5.7%) patients and 3 (3.4%) patients discontinued the study treatment due to AE and SAE, respectively.

Over the 4-year study duration, 7 deaths (2.5%) were reported in the inclisiran group and one death in the switching arm, and none of the deaths was assessed as drug-related.

In ORION-8, [redacted] of patients in each of the inclisiran-only and switching groups reported an AE, and [redacted] of patients who rolled over from the ORION-3 trial. There were also similar numbers of patients who discontinued treatment due to an AE ([redacted]) in the inclisiran-only group and the switching group, versus [redacted] of patients who rolled over from the ORION-3 trial.

With respect to SAE, [redacted] of patients in the inclisiran-only group, [redacted] of patients in the switching group and [redacted] of patients who rolled over from ORION-3 experienced a SAE.

With respect to AE of special interest, the following occurred in the inclisiran-only group, the switching group, and the group who rolled over from ORION-3: [redacted]

Critical Appraisal

The open-label design of ORION-3 and ORION-8 is considered a limitation that could bias the results parameters. Furthermore, only those who completed the parent trials were eligible for participation into these extensions, which might have potentially led to a selection bias. The lack of a control/comparator arm is considered a key constraint that limits the interpretation of study outcomes.

As the ORION-3 and ORION-8 studies consisted of patients who took part in the pivotal studies, it is reasonable to expect that the same strengths and limitations related to generalizability apply to the extension studies, with the additional caveat of potential selection bias due to the enrollment criteria.

Indirect Comparisons

Description of Studies

The sponsor submitted an ITC that compared the efficacy of inclisiran to relevant drug comparators in patients with HeFH or ASCVD (or ASCVD RE). The objective of the sponsor-submitted report was to conduct a feasibility assessment via systematic review of the literature, and if possible, to conduct an indirect comparison evaluating the relative efficacy and safety of inclisiran vs relevant drug comparators including ezetimibe, and other PCSK9 inhibitors in patients with HeFH or ASCVD (or ASCVD RE).

The sponsor submitted ITC was informed by a systematic review of RCTs conducted in April 2020. Thirty-nine studies met the inclusion criteria of the review and feasibility assessment, and 24 studies were subselected for inclusion in the ITC based on network connectivity and homogeneity in study characteristics, patient characteristics, or outcomes that were likely modifiers of the relative treatment effects.

The analyses were conducted using a network meta-analysis (NMA). Selection of both fixed and random effects were conducted for outcomes of interest. Random effects analyses were selected as the base case given the number of studies per node and observed heterogeneity in patient and trial characteristics. Three network scenarios were conducted: HeFH patients on MTD statin, ASCVD and risk equivalent patients on MTD statin, and ASCVD and risk equivalent patients who are intolerant to statins. Efficacy outcomes

included percent, absolute, and time-adjusted change from baseline in LDL-C, and percent change from baseline in HDL-C, and safety outcomes included total discontinuations, and discontinuations due to AEs.

Efficacy Results

A total of seven trials were included in the network for the HeFH population on MTD statins, 13 studies were included in the base case network for the ASCVD and risk equivalent populations on MTD statins, where one closed loop was formed, and seven trials were included in the network for ASCVD and risk equivalent populations intolerant to statins. In the HeFH population on MTD statins, there was no difference between inclisiran and alirocumab or evolocumab for any efficacy and safety outcomes. In the ASCVD and risk equivalent population on MTD statin network, inclisiran was favoured over ezetimibe for efficacy outcomes related to LDL-C, however there was no difference between inclisiran and alirocumab or evolocumab for any efficacy or safety outcomes. In the ASCVD and risk equivalent population intolerant to statin network, inclisiran was favoured over ezetimibe for efficacy outcomes related to LDL-C but not safety outcomes. There was no difference between inclisiran and alirocumab or evolocumab in any efficacy or safety outcomes.

Critical Appraisal

There were several limitations with the key assumptions made in the NMA approach with regards to the background statin use, and the time of assessment of outcomes, impacting clinical and methodological heterogeneity which resulted in limited interpretability and generalizability of the results. Though not reported or accounted for, these assumptions likely impacted treatment effects and the results of each NMA and were a significant source of heterogeneity in the studies. It was assumed in the NMA that individual statins had similar efficacy as background therapy regardless of dose and would not bias the results of the NMA, however, based on discussions with the clinical expert consulted by CADTH, this was not considered a reasonable assumption. It was also assumed that differences in CV risk and severity would not impact the relative effects on LDL-C, and therefore no attempt to adjust for differences in baseline characteristics was conducted due to the number of studies and inconsistent reporting of characteristics. The NMA used 24 weeks as the time of assessment, which was considered acceptable for lipid and lipoprotein outcomes. End of study values for safety were used and considered comparable if the duration of follow-up was 24 weeks or longer. Variations in trial length are bound to influence the number of patients withdrawing for various reasons and given the 24-week time of assessment, may undermine true treatment effects. Additionally, given the biannual dosing regimen of inclisiran, a 24-week time of assessment may be insufficient to assess safety outcomes compared to the Q2W dosing regimen of alirocumab and evolocumab.

Overall, the studies included in the NMA were believed to be statistically heterogeneous based on the considerable I^2, however, it is unclear what the source of heterogeneity was. The observed heterogeneity was likely due to observed and unobserved differences in patient populations across the included studies, data imputation analysis methods, and the specific background treatments allowed and/or delivered. Unidentified or unknown clinical (particularly treatment effect modifiers) or methodological heterogeneity need to be explored, as it is unclear if the transitivity assumption was appropriately met.

In general, all treatments were favoured over placebo for all outcomes in each network scenario, however, the results typically displayed exceedingly wide credible intervals (CrIs), challenging the precision of the results.

Studies Addressing Gaps in the Evidence From the Systematic Review

Pooled Safety Analysis of Seven ORION Trials

Description of Studies

This post hoc analysis comprised patients treated with 300 mg inclisiran sodium or placebo in the completed (ORION-1, -3, -5, -8, -9, -10, and -11) and ongoing (ORION-8) trials. The objective was to obtain data regarding the long-term safety and tolerability of inclisiran for up to 6 years in a large, pooled dataset from seven completed and ongoing trials and diverse sample of patients at risk for CV events. Exposure-adjusted incidence rates and Kaplan-Meier estimates of cumulative incidence of reported treatment-emergent AE, abnormal laboratory measurements, and incidence of antidrug antibodies (ADA) were analyzed.

This analysis included 3576 patients treated with inclisiran for up to 6 years and 1968 patients treated with placebo for up to 1.5 years, with 9982.1 and 2647.7 patient-years of exposure, respectively.

Harms Results

At least one SAE was reported in 32.2% and 22.1% patients in the inclisiran and placebo groups, respectively. The most common SAEs were cardiac, reported in 11.6% and 9.0% patients, respectively. At least one AE led to study drug discontinuation in 3.2% and 1.7% of patients in the inclisiran and placebo groups, respectively.

AEs at the injection site were more frequent with inclisiran (9.3%) compared with placebo (1.8%) groups. AEs at the injection site leading to study drug discontinuation were higher on inclisiran (0.1 per 100 patient-years) than on placebo (0.0 per 100 patient-years).

Kaplan-Meier analyses showed that AEs that were serious or led to discontinuation; hepatic, muscle, and kidney events; incident diabetes; and elevations of creatine kinase or creatinine accrued at a comparable rate between groups for up to 1.5 years, with similar trends continuing for inclisiran beyond this period. Fewer major cardiovascular events reported as AEs occurred with inclisiran during this period. Treatment-induced ADA were uncommon with inclisiran (4.6%), with few of these persistent (1.4%).

Critical Appraisal

Internal Validity

The findings are derived from pooled data from seven clinical trials with specific inclusion criteria, and, thus, patient populations enrolled at different times may have had different clinical characteristics not reflected in the tables of baseline characteristics and may not be fully reflective of a general population. Although EAIRs were calculated, no direct comparison of events with inclisiran versus placebo is possible beyond the first 1.5 years, and only a few patients were exposed to inclisiran for more than 4 years, which limits us to drawing a meaningful conclusion.

External Validity

The pooled data analysis consisted of patients who took part in the pivotal studies, it is reasonable to expect that the same strengths and limitations related to generalizability apply to this study.

Economic Evidence

Cost and Cost-Effectiveness

Copy and paste Table 2 from the PE Report (i.e. “Summary of Economic Evaluation”).

Table 2: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model
Target population	Adult patients with nFH with ASCVD who require additional lowering of LDL-C despite maximally tolerated statin therapy.
Treatment	Inclisiran + standard of care (SoC, defined as maximally tolerated dose of statin therapy ± ezetimibe)
Dose Regimen	284 mg initially, at month 3, and every 6 months thereafter.
Submitted Price	Inclisiran, 284 mg / 1.5 mL, pre-filled syringe: $2,839.28
Treatment Cost	$5,679 per year
Comparators	Standard of care
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs

Component	Description
Time horizon	Lifetime (40 years)
Key data sources	ORION-10, ORION-11, both randomized controlled trials versus placebo Sponsor-submitted NMA
Key limitations	• The relative clinical effectiveness of inclisiran is highly uncertain. While greater reductions in LDL-C may be achieved with inclisiran relative to SoC, there is no evidence to suggest that it is more effective than existing PCSK9 inhibitors. Conclusions for the MACE outcome could not be drawn due to a high risk of bias in the submitted analysis. • The baseline risk of cardiovascular events may not reflect that of the Canadian population given the lack of Canadian-specific data. • The sponsor's probabilistic analysis did not specify any uncertainty with respect to: baseline age, baseline LDL-C, gender, and diabetic status.
CADTH reanalysis results	• The CADTH base case characterized the uncertainty in four input parameters in the probabilistic analysis: baseline age, baseline LDL-C, gender, and diabetic status. • ICER = $77,705 per QALY gained (incremental costs = $59,990; incremental QALYs = 0.77) • A 32% price reduction is required to be considered cost-effective at a willingness to pay threshold of $50,000 per QALY gained.

Budget Impact

CADTH identified the following key limitations with the sponsor's submitted BIA: the comparator prices are uncertain. In the absence of more reliable input values for the BIA, the sponsor's base case was maintained. The net budget impact of inclisiran was estimated to be $344,838,487 in Year 1, $676,139,138 in Year 2, and $826,213,367 in Year 3. The three-year net budget impact was $1,847,190,991.

CDEC Information

Members of the Committee:

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

Meeting date: February 29, 2024

Regrets:

None

Conflicts of interest:

None