

Reimbursement Recommendation

Plozasiran (Redemplo)

Indication: As an adjunct to diet to reduce triglyceride levels for adult patients with familial chylomicronemia syndrome (FCS) for whom standard triglyceride lowering therapies have been inadequate.

Sponsor: Arrowhead Pharmaceuticals, Inc.

Final recommendation: Reimburse with conditions

Summary

What Is the Reimbursement Recommendation for Redemplo?

Canada's Drug Agency (CDA-AMC) recommends that Redemplo be reimbursed by public drug plans for familial chylomicronemia syndrome (FCS) if certain conditions are met.

Why Did CDA-AMC Recommend Reimbursement?

The Canadian Drug Expert Committee (CDEC) determined that Redemplo demonstrates acceptable clinical value versus placebo in patients with FCS. This determination was enough for CDEC to recommend that Redemplo be reimbursed. Given that Redemplo is expected to be an additive treatment to low-fat diet, acceptable clinical value refers to added value versus diet alone.

Evidence from a clinical trial showed that Redemplo given for 12 months improved triglyceride levels and rate of acute pancreatitis in adult patients with FCS. The certainty in the results was moderate due to some imprecision as a result of small sample sizes given the rarity of FCS. Results from the trial about health-related quality of life were inconclusive. Harms data were generally comparable between groups, and few patients discontinued from treatment due to adverse events (AEs).

Redemplo is expected to address some identified unmet clinical needs compared to current standard of care (i.e., off-label therapies). Tryngolza (olezarsen) recently received a positive recommendation from CDA-AMC, and the safety and efficacy of Redemplo compared to Tryngolza is unknown.

Which Patients Are Eligible for Coverage?

Redemplo should only be reimbursed for adult patients with FCS in line with the Health Canada indication.

What Are the Conditions for Reimbursement?

Redemplo should only be reimbursed if patients are diagnosed with FCS based on clinical or genetic assessments as detailed in [Table 1](#), and if the cost of Redemplo is reduced. Because FCS is a rare disease, initiation and management of therapy with Redemplo should be managed by a specialist with expertise in treating FCS. The recommended period for initial reimbursement is 6 months, followed by annual renewals thereafter. Renewal is recommended to be based on an observation of clinical benefit, as demonstrated with a reduction in fasting triglyceride levels, and no signs

Summary

of significant disease worsening that would indicate poor or nonresponse to treatment (i.e., increased rate of acute pancreatitis as judged by the treating clinician).

Review Background

- **Disease background:** FCS is a rare, serious, recessively inherited metabolic disorder in which the body's metabolism does not break down fats correctly due to a deficiency in lipoprotein lipase function. Patients with FCS have severely elevated levels of triglycerides in the blood, causing a high risk of episodes of acute pancreatitis, which can be painful, typically require hospitalization, and are potentially life threatening. The estimated global prevalence is approximately 1 to 10 per million people, although it is more common in some regions of Quebec due to a genetic founder effect.
- **Indication and reimbursement request:** Plozasiran (Redemplo) has been approved by Health Canada “as an adjunct to diet to reduce triglyceride levels for adult patients with familial chylomicronemia syndrome (FCS) for whom standard triglyceride lowering therapies have been inadequate.” The sponsor is seeking reimbursement for this patient population.
- **Drug under review:** Plozasiran is a double-stranded interfering ribonucleic acid inhibitor of APOC3. It is available as 25 mg/0.5 mL sterile solution and the dosage recommended in the product monograph is 25 mg administered as a single subcutaneous injection every 3 months.
- **Treatment costs:** At the submitted price of \$135,549.38 per 0.5 mL prefilled syringe, the annual cost of plozasiran is expected to be \$542,198 per patient, based on the Health Canada–recommended dosage.

Highlights of Input From Interested Parties

The patient group, the Canadian Organization for Rare Disorders, noted the following regarding impacts of the disease, unmet needs, and important outcomes:

- Patients with FCS and their caregivers highlighted that severe dietary restrictions, life-threatening complications, episodes of acute pancreatitis, and the associated severe pain and hospitalizations contribute to a profound burden of illness on their quality of life. Some patients expressed feeling very isolated due to not being able to share meals with family, friends, or work colleagues, as well as complications in their home and work lives as a result of disease-related flare-ups and highly restrictive lifestyle-based management.
- Patients with FCS often experience delayed diagnosis or misdiagnosis due to the disease being rare and unknown among medical professionals, and because the disease can present with nonspecific symptoms such as recurrent abdominal pain, fatigue, malaise, and brain fog. Patients with late diagnoses described dismissal by medical professionals of their nonspecific symptoms like fatigue and stomach aches throughout life, ineffective treatments, and stigma from doctors due to being mistaken for a person with alcohol dependency and/or due to a lack of knowledge about this rare condition.
- Patients with FCS have severely elevated fasting triglyceride levels that typically do not respond to conventional management strategies, including lifestyle changes, diet, alcohol abstinence, nor to pharmacological therapies such as statins and fibrates, because of the underlying mechanism of

the disease. Because there are currently no available therapies for the treatment of FCS in Canada, many patients try off-label therapies with no supportive evidence in FCS that are known to be ineffective.

- Patients with FCS and their caregivers highlighted that treatment goals include reduction of triglyceride levels with few side effects and prevention of future episodes of pancreatitis. They also expressed need for a therapy that has a minimally disruptive administration schedule and that does not require travel for those living far from specialty centres. Patients would also like a therapy that allows them to relax the restricted diet such that they could partake in social events without anxiety of severe medical consequences.

The clinical experts consulted by CDA-AMC noted the following regarding unmet needs arising from the disease and place in therapy for the drug under review:

- FCS is a rare, serious, genetic disease that causes substantial morbidity and mortality and for which current standard of care relies on off-label therapies that are known to be ineffective in FCS.
- The primary treatment goal is to reduce fasting serum triglycerides, followed by the reduction in episodes of acute pancreatitis. Other secondary goals include reduction of abdominal pain and other symptoms.

The participating public drug programs raised potential implementation issues related to considerations for initiation, renewal, discontinuation, and prescribing of therapy; care provision issues; and system and economic issues.



Person With Lived Experience

A person with lived experience from Quebec shared his lifelong journey living with FCS, which he has had since early adulthood but was not clearly diagnosed at the time. He described experiencing episodes of pancreatitis, including a severe event requiring a lengthy recovery that significantly affected his life and career. He emphasized the ongoing burden of strict dietary restrictions, complete avoidance of alcohol, and feeling socially isolated due to these limitations. He noted that fear of pancreatitis was constant, particularly when far from a hospital. Despite this, he remained physically active and continued his professional work. He highlighted the positive impact of his current treatment, plogasiran, which involves periodic injections and monitoring but has eliminated symptoms. During the question and answer session, he emphasized that treatment reduced his fear of pancreatitis and allowed him to feel more confident living without needing to remain close to hospital care.

Note: The perspectives shared by people with lived experience who present to the committee reflect their individual experiences and are not necessarily representative of all people with the same condition or course of treatment. Their insights provide valuable context about what a patient, support person, or caregiver might go through with this condition or treatment, helping to inform the committee's deliberations. These narratives complement other forms of evidence and input and should be considered as 1 element contributing to a broader understanding of the condition and treatment under review.

Recommendation

With a vote of 15 to 0, CDEC recommends that plozasiran be reimbursed “as an adjunct to diet to reduce triglyceride levels for adult patients with familial chylomicronemia syndrome (FCS) for whom standard triglyceride lowering therapies have been inadequate,” only if the conditions listed in [Table 1](#) are met.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Treatment with plozasiran as an adjunct to diet should be reimbursed when initiated in patients aged 18 years and older who are diagnosed with FCS.	Evidence from the PALISADE trial suggested that treatment with plozasiran resulted in a clinical benefit compared to placebo in adult patients with FCS, for whom standard triglyceride-lowering therapies have been inadequate.	Adherence to low-fat diet: The clinical benefit of treatment with plozasiran was demonstrated in combination with a low-fat diet. According to input from the clinical experts, ongoing adherence to a strict low-fat diet is essential.
2. Diagnosis of FCS based on a documented history of fasting triglyceride levels > 1,000 mg/dL (11.3 mmol/L) on repeat testing (≥ 3 prior occasions) and at least 1 of the following: 2.1. Supportive genetic test 2.2. History of recurrent episodes of acute pancreatitis not caused by alcohol or cholelithiasis 2.3. History of recurrent hospitalizations for severe abdominal pain without other explainable cause 2.4. History of childhood pancreatitis 2.5. Known lipoprotein lipase deficiency 2.6. Family history of high triglyceride-induced pancreatitis.	The PALISADE trial enrolled adult patients with a diagnosis of FCS that was based on a clinical diagnosis or genetic confirmation. The recommended initiation criteria are consistent with the identification of patients with FCS in the PALISADE trial, and reflective of clinical practice in Canada.	Initiation criteria for treatments for FCS: If olezarsen is covered by public drug plans, the drug plans may consider aligning the criteria of plozasiran and olezarsen. This includes genetic confirmation of FCS as the primary basis for diagnosis, with eligibility criteria applied to minimize unnecessary variation in access, particularly for patients with a confirmed genetic diagnosis. Triglyceride levels: The threshold of 1,000 mg/dL (11.3 mmol/L) is based on the inclusion criteria for the PALISADE clinical trial. Based on clinical expert input, a threshold of 10 mmol/L is commonly used as a component of the diagnosis of FCS in Canada and is commonly cited as a threshold for severe risk of acute pancreatitis. The drug plans could consider requiring levels of at least 10 mmol/L to align with current clinical practice in the management of FCS. Prior therapy: Inadequate management of triglyceride levels with prior therapy is defined as triglyceride levels of ≥ 10 mmol/L despite at least 6 months of a low-fat diet and prior treatment with standard lipid-lowering drugs (e.g., statins or fibrates, and so forth) for at least 1 week to 1 month. Hemoglobin A1C: Adequate control of hemoglobin A1C may vary between patients but generally can be considered a hemoglobin A1C measurement of ≤ 8.5%.

Reimbursement condition	Reason	Implementation guidance
3. Duration of initial authorization is 6 months.	The primary outcome of the PALISADE trial was the percent change in fasting triglyceride levels from baseline at 10 months. However, assessment of response at 6 months is consistent with clinical practice in Canada based on expert input.	Documentation at baseline: The fasting triglyceride levels and the annualized frequency of acute pancreatitis should be documented at baseline before initiating treatment to inform the renewal criteria.
Renewal		
4. Renewal after initial authorization and subsequent renewals should be assessed annually.	Annual assessments will help ensure the treatment is used for those benefiting from the therapy and would reduce the risk of unnecessary treatment.	—
5. For renewal after initial and subsequent authorization, documentation of beneficial clinical effects is required when requesting continuation of reimbursement. Beneficial clinical effects are defined by all of the following: 5.1. A reduction in triglycerides compared to baseline that is considered clinically meaningful according to the treating clinician. 5.2. No substantial worsening of pancreatitis due to FCS according to the treating clinician.	The percent change in fasting triglyceride levels from baseline to month 10 was the primary end point in the PALISADE trial. The percent change from baseline to month 12 in the plogasiran treatment group was an LS mean of -80.1% (IQR, -89.9% to -61.0%). Based on clinical expert input, a reduction in triglyceride levels between 10% to 30% may be meaningful, but there is no defined threshold in patients with FCS.	Lifestyle and risk factor management: Adherence to a low-fat diet, alcohol abstinence, and management of other triglyceride-elevating conditions must be maintained during treatment with plogasiran. Significant worsening of pancreatitis: One of the most important goals of treatment for patients with FCS is to reduce the risk of acute pancreatitis. CDEC acknowledged that the frequency of events of acute pancreatitis can be unpredictable and may vary between patients or over time. Therefore, significant worsening of pancreatitis should be based on clinician judgment.
Prescribing		
6. Plogasiran must be prescribed by specialists with experience in the diagnosis and management of FCS.	This is meant to ensure that plogasiran is prescribed for appropriate patients. FCS is a rare and serious condition requiring expertise in management.	Shared-care models featuring virtual consultations and local monitoring may be appropriate approaches for patients with geographical challenges in accessing specialist facilities, due to the scarcity of experts across Canada, especially outside of Quebec. Relevant specialties might include but are not limited to endocrinology, cardiology, lipidology, medical biochemistry, and internal medicine.
7. Plogasiran should not be prescribed in combination with olezarsen.	There is no evidence to support this combination.	Plogasiran and olezarsen have similar mechanisms of action.
Pricing		
8. A reduction in price.	Using the CDA-AMC base-case analysis, the ICER for plogasiran plus SOC was \$1,813,089 per QALY gained when compared with SOC alone in the indicated	The CDA-AMC analysis is based on public list prices for all treatments. Further price reductions may be required if there are price arrangements (discounts)

Reimbursement condition	Reason	Implementation guidance
	population. A band 4^a price reduction would be required to achieve cost-effectiveness at a \$50,000 per QALY threshold. A band 4^a price reduction would be required to achieve cost-effectiveness at a \$100,000 per QALY threshold. Exact price reductions at any given willingness-to-pay threshold can be found in the CDA-AMC main report and Supplemental Material document. Cost-effectiveness relative to olezarsen in the indicated population is unknown given the lack of evidence regarding comparative efficacy and safety. To ensure cost-effectiveness, plozasiran should also be priced no higher than olezarsen when reimbursed in the indicated population.	currently in place or under negotiation for any treatment included in the economic analysis. At the time of this recommendation, olezarsen is under consideration for negotiation following a positive recommendation conditional to price reduction, for reimbursement in the indicated population. Cost of genetic testing: Cost of genetic testing was not considered in the economic model or BIA model. Given the limited availability of genetic testing for FCS and the cost burden that implementation would place on public health care systems, CDEC recommends that the sponsor be required to cover the cost of these tests across Canada and to ensure its availability where needed.

BIA = budget impact analysis; CDA-AMC = Canada's Drug Agency; CDEC = Canadian Drug Expert Committee; FCS = familial chylomicronemia syndrome; ICER = incremental cost-effectiveness ratio; IQR = interquartile range; LS = least square; QALY = quality-adjusted life-year; SOC = standard of care.

^aFor the statement regarding the size of the price reduction required, band 1 = 1% to 24%, band 2 = 25% to 49%, band 3 = 50% to 74%, and band 4 = 75% or greater.

Rationale for the Recommendation

Clinical Value

Based on the totality of the clinical evidence, CDEC concluded that plozasiran demonstrates acceptable clinical value in patients with FCS. Given that plozasiran is expected to be an additive treatment to a low-fat diet, acceptable clinical value refers to added value versus diet alone. Current management of FCS in Canada, outside of clinical trials, includes off-label therapies such as statins, fibrates, and omega-3 fatty acids that are typically less effective in lowering triglyceride levels in patients with FCS; these therapies might also be concurrently used with plozasiran in clinical practice.

Evidence from 1 phase III randomized controlled study (PALISADE; N = 75) demonstrated that plozasiran 25 mg likely results in a clinically important reduction in fasting triglyceride levels at month 10 and at month 10 and 12 (averaged) compared to placebo. From baseline to 10 months, the between-group difference in least squares mean change in fasting triglycerides was -58.7% (95% confidence interval [CI], -89.6% to -27.9%; P < 0.0001), and from baseline to the average of month 10 and 12 it was -59.6% (95% CI, -91.6% to -27.5%; P < 0.0001), both favouring plozasiran. Treatment with plozasiran likely also results in a clinically meaningful decrease in the proportion of patients who experience events of acute pancreatitis over a 12-month period. Positively adjudicated events of acute pancreatitis occurred in 2 patients (7.7%) in the plozasiran 25 mg group (N = 26) and 5 patients (20.0%) in the placebo group (N = 25). The odds ratio was

Patients and clinicians identified substantial unmet needs given that there are no approved therapies indicated for the treatment of FCS that are currently reimbursed. The key unmet needs include a safe and tolerable therapy that can meaningfully reduce triglyceride levels and reduce the rate, or prevent episodes, of acute pancreatitis. CDEC concluded that plozasiran likely meets these needs, but the committee was unable to draw conclusions on health-related quality of life due to inconclusive results in the PALISADE study.

Further information on the committee's discussion around clinical value is provided in the Summary of Deliberation section.

The determination of acceptable clinical value was sufficient for CDEC to recommend reimbursement of plozasiran. As part of the deliberation on whether to recommend reimbursement, the committee also considered unmet clinical need, unmet nonclinical need, and health inequity. Information on this discussion is provided in the Unmet Clinical Need and Distinct Social and Ethical Considerations domains in the Summary of Deliberation section.

Summary of Deliberation

The committee considered the following key discussion points, organized by the 5 domains of value.



- **Appropriate comparators:** At the time the submission was received, there were no approved therapies for FCS reimbursed by public drug plans. As such, placebo, in addition to a low-fat diet (≤ 20 mg of fat per day), was considered an appropriate comparator for plogasiran as an adjunct to

diet. Although many patients receive off-label therapies such as statins, omega-3 fatty acids, and fibrates, these are not expected to be effective in sufficiently lowering triglycerides or preventing pancreatitis in patients with FCS.

- Relevance of olezarsen as a comparator:** Due to the timing of the submission, olezarsen (Tryngolza) was still undergoing pan-Canadian Pharmaceutical Alliance (pCPA) negotiation and comparisons between plozasiran and olezarsen are not available in terms of efficacy, safety, or economic impacts. If both olezarsen and plozasiran are reimbursed in the future, this is an important evidence gap because both therapies are expected to occupy a similar place in the treatment pathway of FCS. The committee heard from the clinical experts that the choice between olezarsen and plozasiran, if both were equally accessible, would be highly individual and could differ based on patient preferences around the dosing schedule (once monthly for olezarsen versus once every 3 months for plozasiran) and the differences in the safety profiles and risks associated with each therapy.
- Initiation criteria of plozasiran versus olezarsen:** There are important differences in the patient eligibility criteria for the pivotal trials of olezarsen (the BALANCE study) and plozasiran (the PALISADE study), most notably that the BALANCE study required genetic confirmation of diagnosis while the PALISADE study enrolled patients based on a clinical diagnosis or with genetic confirmation of FCS. The initiation criteria recommended for olezarsen reflect this and recommend that genetic testing must be conducted, although patients with negative or inconclusive results can be reimbursed if they meet other clinical criteria. Because one-half of the patients in the PALISADE study had clinical diagnoses and were not genetically confirmed, and the genetic test is not comprehensive of all known or unknown causes of FCS, the committee decided that requiring genetic testing for reimbursement of plozasiran was not mandatory. However, given that plozasiran and olezarsen have similar mechanisms of action, are expected to occupy the same place in therapy, and are expected to have a similar efficacy and safety profiles according to clinical expert opinion, the drug plans may wish to consider aligning the reimbursement criteria between the 2 treatments. A request for advice to CDA-AMC may also be considered by the drug plans to inform appropriate criteria and the feasibility of alignment of the initiation criteria between plozasiran and olezarsen.
- Efficacy versus placebo:** Evidence from 1 phase III randomized controlled study (PALISADE; N = 75) demonstrated that plozasiran 25 mg likely results in a clinically important reduction in fasting triglyceride levels at month 10 and at month 10 and 12 (averaged) compared to placebo. From baseline to 10 months, the between-group difference in least squares mean change in fasting triglycerides was -58.7% (95% CI, -89.6% to -27.9%; $P < 0.0001$), and from baseline to the average of month 10 and 12 was -59.6% (95% CI, -91.6% to -27.5%; $P < 0.0001$), both favouring plozasiran. Treatment with plozasiran likely also results in a clinically meaningful decrease in the proportion of patients who experience events of acute pancreatitis over a 12-month period. Positively adjudicated events of acute pancreatitis occurred in 2 patients (7.7%) in the plozasiran 25 mg group (N = 26) and 5 patients (20.0%) in the placebo group (N = 25). The odds ratio was [REDACTED] and the relative risk was [REDACTED]. No new safety signals

were identified in the PALISADE study or the open-label extension. There was uncertainty in the results due to imprecision and the small sample size.

- Clinical importance of treatment effects:** The committee concluded that the benefit in triglyceride reduction and rate of acute pancreatitis was likely clinically important in magnitude based on patient group input, clinician group input, and clinical expert input. There was uncertainty in both end points due to imprecision. Reducing or preventing acute pancreatitis events were clinically important end points identified by patients and clinicians, though the magnitude of benefit observed in the PALISADE study is also uncertain because of the challenge of evaluating an uncommon event in a small patient population over a limited duration of time. Compared to placebo over 12 months, treatment with plogasiran 25 mg may improve health-related quality of life, as measured by the altered bowel habit and health care satisfaction domains of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Pancreatic Cancer Module (EORTC QLQ-PAN26), but may result in little to no difference in the digestive and pancreatic pain domains. However, this module was not developed for and has not been validated in a population with FCS, so it is unknown if the scale is adequately valid and sensitive in this population. Finally, treatment with plogasiran 25 mg may result in little to no difference in serious AEs compared to placebo.
- Certainty of the evidence:** The committee recognized FCS as a rare disease and the corresponding potential for uncertainty in the trial design. For example, the pivotal study and supportive studies each had small sample sizes and there was imprecision in the results; however, the primary and key secondary end points were controlled for multiplicity, which potentially offset some of the uncertainty in the results due to the small sample size. Overall, it was concluded that in the Grading of Recommendations Assessment, Development and Evaluation assessment, the certainty of the evidence was moderate for the primary and secondary end points (triglycerides and acute pancreatitis), low for health-related quality of life end points, and low for serious AEs.
- Clinical diagnoses:** The committee heard that current clinical practice in the diagnosis of FCS is based on clinical judgment and that specialists are required to diagnose FCS. The pivotal PALISADE study included patients with and without genetic confirmation of FCS diagnosis and, with the caveat that the study was not powered to detect differences in subgroups, there appeared to be clinically meaningful magnitudes of benefit associated with treatment with plogasiran in both groups. This was aligned with the expectations of the clinical experts who stated that, based on prior experience with volanesorsen (which is not approved for use in Canada but has a similar mechanism of action to olesarsen and plogasiran), patients with or without genetic confirmation of diagnosis are not expected to differ in treatment response.
- Long-term safety and efficacy:** An ongoing, phase III, multicentre, open-label extension of the PALISADE study was submitted as supportive evidence. Interim results did not reveal any additional safety concerns; however, the ability to draw conclusions from it was limited by few patients, interim data, and the lack of a comparator group.
- Renewal criteria:** In consultation with the advising clinical expert, the committee discussed that renewal of reimbursement for plogasiran is appropriate in circumstances where the triglyceride

levels of the patient are meaningfully lower after receiving the therapy. The clinical expert estimated that clinicians may consider a reduction between 10% and 30% to be a minimal clinically important lowering of triglyceride levels; however, a specific threshold for adequate response is difficult to quantify in the absence of evidence. The committee also discussed that preventing or reducing the rate of events of acute pancreatitis is a high priority, but that events may still occur during treatment with plogasiran for a variety of reasons. However, if there are signs of nonresponse to the therapy, including a lack of substantial lowering of triglyceride levels or an apparent worsening of the rate of pancreatitis, it would be appropriate to discontinue treatment.

- **Clinical value:** Based on all of the preceding considerations, the committee determined there was added clinical value associated with plogasiran as an adjunct to diet and standard of care in Canada versus diet and standard of care.



Unmet Clinical Need

- **Input on unmet clinical need:** Patients with FCS and their caregivers identified a need for a safe and tolerable treatment that can effectively reduce the elevated serum triglycerides and acute pancreatitis risk associated with FCS. Clinician group input and clinical experts consulted by CDA-AMC for this review concurred that despite intensive lifestyle interventions and commonly used off-label pharmacotherapies (such as statins), significant unmet needs persist. The clinician group input highlighted that there is a critical need for a targeted, well-tolerated, and effective treatment that can reduce chylomicron levels, prevent pancreatitis, improve daily symptoms, and reduce the overall burden on patients and caregivers.
- **Severity of the disease:** The committee recognized the clinical expert input that FCS is a genetic, lifelong condition in which patients have severely elevated triglycerides and are at an increased risk of recurring acute pancreatitis, which can be a serious, life-threatening event requiring hospitalization. The clinical experts highlighted that many patients have recurrent hospitalizations and that mortality associated with FCS is primarily related to multiorgan failure or other sequelae of pancreatitis. Despite adherence to a restrictive diet, patients may still experience recurrent pancreatitis and downstream complication thereof which may include exocrine pancreatic insufficiency, type IIIC diabetes, and chronic pancreatitis.
- **Availability of treatment options:** Until recently, there were no therapies indicated for the treatment of FCS in Canada. Besides plogasiran, olezarsen is the only therapy indicated for the treatment of FCS in Canada, and it is currently under negotiation with pCPA and may not yet be widely accessible for patients with FCS. The future reimbursement decisions around olezarsen are currently unknown. The clinical experts and clinician group input described that current management relies on an extremely restrictive diet of 20 g of fat or less per day, but patients still experience symptoms, severely elevated triglycerides, and an elevated risk of pancreatitis despite adherence. Off-label pharmacotherapies such as statins, fibrates, and omega-3 fatty acids are often used with little to no clinical benefit.

- **Significant unmet clinical need:** Due to challenges with evidence generation associated with the rarity of FCS, the severity of the disease, and the lack of effective treatment options, CDEC considered there to be significant unmet need as described in the recommendation framework in the [Procedures for Reimbursement Reviews](#).



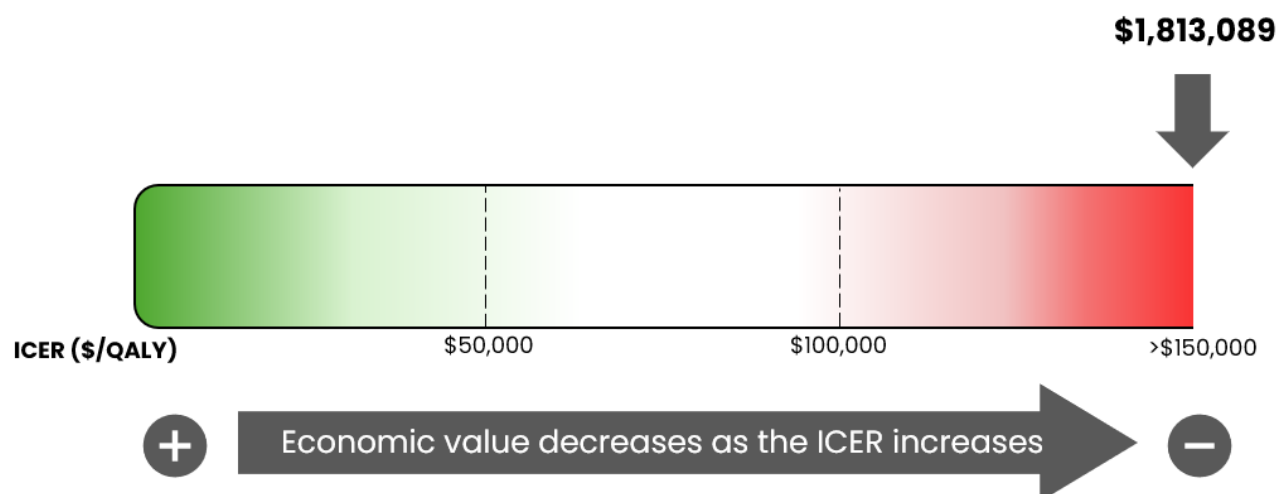
Distinct Social and Ethical Considerations

- **Input on unmet nonclinical need:** The committee acknowledged that the restrictive diet requiring 20 g of dietary fat or less per day is difficult to adhere to and impacts a patient's ability to participate in social events related to food according to patient and clinician group inputs and the clinical experts consulted for this review. Patients also described facing stigma, lack of understanding about the importance of the diet from family, friends, and work colleagues due to the rarity and lack of knowledge of FCS. The committee heard that patients frequently face stigma, delayed diagnosis, misdiagnosis (with more common conditions), and dismissal of nonspecific symptoms by medical professionals for the same reasons.
- **Significant unmet nonclinical need:** The committee determined that there was a significant unmet nonclinical need but that plozasiran is not likely to address these needs because the drug is intended to be prescribed in conjunction with a low-fat diet and will not directly impact the knowledgeability of medical professionals or the general population about FCS. However, the committee heard from the patient group input that patients with experience receiving plozasiran felt less burden, stress, and anxiety regarding the potential for medical emergencies resulting from small mistakes in diet.



Economic Considerations

- **Health impacts of plozasiran versus relevant comparators:** Plozasiran is predicted to be associated with a gain of 0.57 life-years compared to best supportive care (BSC) and may result in a gain of 1.93 quality-adjusted life-years (QALYs) compared to BSC over a lifetime horizon (54 years).
- **Cost of plozasiran versus relevant comparators:** Plozasiran is predicted to be associated with higher costs to health care systems than BSC (incremental costs = \$3,489,795) over lifetime horizon (54 years), primarily driven by increased costs associated with drug acquisition of plozasiran.
- **Key findings of the economic evaluation:** Based on the submitted evidence using the sponsor's cost-utility analysis, the CDA-AMC base-case analysis estimated that the incremental cost-effectiveness ratio (ICER) for plozasiran in adult patients with FCS for whom standard triglyceride-lowering therapies have been inadequate was \$1,813,089 per QALY gained when compared with BSC ([Figure 1](#)).

Figure 1: Estimate of the ICER Used by CDEC to Inform the Price Condition

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

- **Certainty of the evidence:** The estimated ICER was highly sensitive to the uncertainty around the direct protective treatment effect on acute pancreatitis risk by plozasiran. Additionally, olezarsen has received Health Canada approval as an adjunct to diet for the treatment of FCS in adults and has been issued a recommendation for reimbursement conditional to price reductions. It is currently under consideration for negotiation through the pCPA for drug plan listing. In the absence of direct or indirect comparative evidence between plozasiran and olezarsen, the cost-effectiveness of plozasiran relative to olezarsen cannot be established. Remaining uncertainty in the clinical data informing the cost-utility analysis, the lack of long-term data, and the evolving reimbursement landscape with the potential availability of olezarsen indicates that further price reductions may be warranted.
- **Other considerations:** The sponsor submitted an additional cost-effectiveness analysis adopting a societal perspective. In this analysis, the sponsor's approach to estimating productivity loss and caregiver health-related quality of life outcomes was uncertain due to a lack of relevant data. As a result of the lack of evidence relating to the impact of treatment for patients with FCS on these outcomes, CDA-AMC was unable to present an analysis from the societal perspective.

Impacts on Health Systems

- **Anticipated budget impact:** If funded, CDA-AMC estimated that 44 patients are expected to receive plozasiran plus BSC by year 3 of reimbursement. CDA-AMC estimates that the budget impact of reimbursing plozasiran plus BSC for the indicated population will be approximately \$24 million over the first 3 years of reimbursement compared to the amount currently spent on BSC, with an estimated expenditure of \$24 million on plozasiran over this period (i.e., BSC costs are assumed to be \$0).

CDEC noted that the magnitude of uncertainty in the budget impact must be addressed to ensure the feasibility of adoption, given the difference between the sponsor's estimate and the CDA-AMC estimate for some scenario analysis. The estimated budget impact is uncertain and will depend on the prevalence of the condition, public coverage for rare disease treatments, market uptake of plozasiran, and its negotiated price.

- **Testing procedure considerations:** The committee discussed that FCS is a genetic disease with some, but not all, known causative mutations in a suite of genes related to lipid metabolism. Based on clinical expert input, it is anticipated that approximately 20% to 50% of patients with FCS could have inconclusive genetic testing results due to causative mutations not captured by gene panels. CDEC recognized that the genetic test is not comprehensive and is not necessary for the diagnosis of FCS for treatment with plozasiran, given that there is evidence of a clinical benefit for both patients with a clinical diagnosis and genetic confirmation. The committee also noted that genetic testing is not consistently available or funded across jurisdictions in Canada and is primarily available through out of country testing. Cost of genetic testing was not considered in the economic model or budget impact analysis model. No major impacts are anticipated, since genetic testing is not required for diagnosis and patient numbers are expected to remain small.

Sources of Information Used by the Committee

To make its recommendation, the committee considered the following information (links to the full documents for the review can be found on the [project webpage](#)):

- the CDA-AMC review of the clinical and pharmacoeconomic evidence submitted by the sponsor, as well as relevant ethical issues related to plozasiran (refer to the main report and Supplemental Material document)
- the sponsor's comments on the draft report and the responses from CDA-AMC
- patients' perspectives gathered by 1 patient group, the Canadian Organization for Rare Disorders (refer to the Patient and Clinician Group Input document)
- input from a person with lived experience who delivered a brief presentation and answered questions from the committee (refer to the Person with Lived Experience section earlier in this document)
- input from public drug programs that participate in the reimbursement review process (refer to the Supplemental Material document)
- input from 2 clinical experts and 1 panellist with expertise in the management of FCS consulted by CDA-AMC.

Special thanks: CDA-AMC extends our special thanks to the individuals who presented directly to CDEC, and to the patient organizations representing the community of those living with FCS, including the Canadian Organization of Rare Diseases, which includes Jida El Hajjar and Jacques Gagnon.

General note: CDA-AMC makes every attempt to engage with people with lived experience as closely to the indication under review as possible; however, at times, CDA-AMC is unable to do so and instead engages with individuals with similar treatment journeys to ensure lived experience perspectives are included and considered in Reimbursement Reviews. CDA-AMC is fortunate to be able to engage with individuals who are willing to share their treatment journeys with CDEC.

CDEC Information

Members of the Committee

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Meeting date: May 28, 2026

Regrets: None

Conflicts of interest: None



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