Canadian Journal of Health Technologies
January 2024 Volume 1 Issue 4

CADTH Reimbursement Recommendation

Calaspargase Pegol (Asparlas)

Indication: As a component of a multi-agent chemotherapeutic regimen for the treatment of acute lymphoblastic leukemia in pediatric and young adult patients age 1 to 21 years

Sponsor: Servier Canada Inc.

Final recommendation: Reimburse with conditions

Summary

What Is the CADTH Reimbursement Recommendation for Asparlas?

CADTH recommends that Asparlas be reimbursed by public drug plans as a component of a multiagent chemotherapeutic (MAC) regimen for the treatment of acute lymphoblastic leukemia (ALL) in pediatric and young adult patients age 1 to 21 years if certain conditions are met.

Which Patients Are Eligible for Coverage?

Asparlas should only be covered to treat children and young adults with ALL.

What Are the Conditions for Reimbursement?

Asparlas should only be reimbursed as part of a MAC regimen. Asparlas should be prescribed by clinicians with expertise in the management of ALL, and the cost of Asparlas should not exceed the drug program cost of treatment with pegaspargase.

Why Did CADTH Make This Recommendation?

- Evidence from 2 clinical trials suggested that IV infusions every 3 weeks with Asparlas is similarly effective as IV infusions every 2 weeks with pegaspargase in terms of achieving adequate asparagine depletion, overall survival (OS), and time until disease progression or death.
- Asparlas may meet needs identified by patients, such as comparable efficacy as existing treatment, manageable side effects, and an extended shelf life, which may support a more stable supply and less frequent drug administration.
- Based on CADTH's assessment of the health economic evidence, Asparlas does not represent good value to the health care system at the public list price. The committee determined that there is not enough evidence to justify a greater cost for Asparlas compared with pegaspargase.
- Based on public list prices, Asparlas is estimated to cost the public drug plans approximately $4.6 million over the next 3 years.

Additional Information

What Is ALL?

ALL is a type of cancer in which cancer cells grow in the bone marrow, blood, and other organs. ALL is most common in young children. The symptoms of ALL are variable and may include bruising, bleeding, shortness of breath, dizziness, anemia, and pain.

Unmet Needs in ALL

Current treatment for ALL in Canada comprises MAC regimens that include pegylated asparaginase (i.e., pegaspargase). However, there is a need for treatments with a consistent supply of asparaginase, and Asparlas, with its extended shelf life and longer dosing interval, may address that need.

How Much Does Asparlas Cost?

Treatment with Asparlas is expected to cost approximately $52,093 per patient per treatment course (7 doses, per the Children's Oncology Group [COG] AALL07P4 trial protocol).

Recommendation

The CADTH pan-Canadian Oncology Drug Review Expert Review Committee (pERC) recommends that calaspargase pegol be reimbursed as a component of a MAC regimen for the treatment of ALL in pediatric and young adult patients age 1 to 21 years, only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

Evidence from 2 phase II, multicentre, open-label trials, COG AALL07P4 (N = 166) and Dana-Farber Cancer Institute (DFCI) 11-001 (N = 239), demonstrated that treatment with calaspargase pegol as a component of a MAC regimen may result in similar clinical benefit to pegaspargase in pediatric and young adult patients with ALL. Results for serum asparaginase activity (SAA), the primary outcome in DFCI 11-001, suggested that calaspargase pegol may be as effective as pegaspargase in achieving complete asparagine depletion and prolonged asparaginase activity. Eighteen days after the induction dose, the percentage of patients with SAA levels at or above 0.1 IU/mL, the predetermined therapeutic threshold, was [redacted] and [redacted] in the calaspargase pegol and pegaspargase groups, respectively. Secondary efficacy end points were supportive of the results for SAA observed with calaspargase pegol. At a median follow-up time of approximately [redacted] months and [redacted] months in COG AALL07P4 and DFCI 11-001, respectively, results for overall, event-free, and disease-free survival were suggestive of little to no difference compared to pegaspargase. In addition, results in both trials suggested similar efficacy compared to pegaspargase based on end-induction minimal residual disease (MRD) and complete remission (CR) status. No new safety concerns were observed with calaspargase pegol. Overall, adverse events (AEs) appeared to be reflective of each trial's backbone

chemotherapies and asparaginase administration schedule. Health-related quality of life (HRQoL) was not assessed in COG AALL07P4 or DFCI 11-001.

Patients identified a need for effective treatments that have manageable side effects, improve quality of life, and ensure a more reliable drug supply and less frequent drug administration. pERC concluded that calaspargase pegol may meet some of the patients' needs as it likely has similar efficacy outcomes to existing treatment, a manageable toxicity profile, and an extended shelf life, which may support a more stable supply and less frequent drug administration (every 3 weeks versus every 2 weeks with continuous asparagine depletion schedules). Although patients expressed an unmet need for treatments that improve quality of life, the effect of calaspargase pegol on HRQoL in patients with ALL is unknown.

Using the sponsor-submitted price for calaspargase pegol and the sponsor-provided price for pegaspargase, calaspargase pegol was determined to be more costly than pegaspargase. As there is insufficient evidence to suggest calaspargase pegol is more effective than pegaspargase, the total drug cost of calaspargase pegol should not exceed the total drug cost of pegaspargase.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
Treatment with calaspargase pegol should be reimbursed in patients aged 1 to 21 years who have ALL.	Evidence from the COG AALL07P4 and DFCI 11-001 trials demonstrated that treatment with calaspargase pegol as a component of a MAC regimen may result in similar clinical benefit when compared to pegaspargase in children and young adults with ALL. This condition is aligned with the indication approved by Health Canada.	—
Discontinuation		
1. Calaspargase pegol should be discontinued in patients who exhibit any of the following: 1.1. development of hypersensitivity reaction or silent inactivation to calaspargase pegol 1.2. development of other high-grade toxicities (e.g., pancreatitis, thrombosis, and hepatotoxicity) 1.3. evidence of disease progression.	No evidence was identified to demonstrate that continuing treatment with calaspargase pegol in patients whose disease has progressed is effective.	The continuous monitoring for silent inactivation, as well as disease progression, and the development of toxicities was considered a best clinical practice point based on clinical expert consensus. To reliably assess the development of hypersensitivity or silent inactivation, SAA levels should be monitored; however, it is acknowledged that this test might not always be available or feasible in different settings across Canada.
Prescribing		
Calaspargase pegol should be prescribed as part of a MAC regimen in replacement of pegaspargase.	In the COG AALL07P4 and DFCI 11-001 trials, calaspargase pegol was administered as part of a MAC regimen.	—

Reimbursement condition	Reason	Implementation guidance
Calaspargase pegol should be prescribed by clinicians with expertise in the management of ALL.	This ensures that calaspargase pegol is prescribed only for appropriate patients and adverse effects are managed in an optimized and timely manner.	—
Pricing		
The cost of calaspargase pegol should be negotiated so that it does not exceed the drug program cost of treatment with pegaspargase.	There is insufficient clinical evidence to justify a cost premium for calaspargase pegol over pegaspargase.	—

ALL = acute lymphoblastic leukemia; COG = Children's Oncology Group; DFCI = Dana-Farber Cancer Institute; MAC = multiagent chemotherapeutic; SAA = serum asparaginase activity.

Discussion Points

- pERC deliberated on the unmet therapeutic needs raised by patients and clinical experts. pERC discussed that ALL is a relatively uncommon blood cancer that mainly affects young children but also occurs in adults. pERC noted that the goal of treatment is curative and comprises MAC regimens that incorporate asparaginase therapy as established standard of care. Clinical experts noted that supplies of current asparaginase treatment (pegaspargase) have not been reliable in meeting the needs of all patients, compounded by the drug's relatively short shelf life. pERC discussed that drug supply disruption may lead to stressful situations for patients and their caregivers. pERC acknowledged that there is a need for effective treatments with tolerable toxicity that improve drug supply chain challenges. Calaspargase pegol with its extended shelf life may address that need. pERC agreed with the clinical experts that calaspargase pegol's triweekly dosing may be more convenient than pegaspargase' biweekly dosing when used with continuous asparagine depletion schedules.
- pERC noted that patients with Philadelphia chromosome (Ph) positive disease were excluded from the available evidence and a minority of patients had Down syndrome and T-cell ALL. pERC acknowledged input from the clinical experts noting that pediatric patients with Ph positive disease who receive tyrosine kinase inhibitor therapy are currently treated with asparaginase-based treatment in clinical practice with no toxicity concerns. pERC agreed with the clinical experts that generalizing the available evidence to patients with T-cell ALL, pediatric patients with Ph positive disease, and patients with Down syndrome may be reasonable. It is unlikely that there will be trials specifically designed for this small group of patients and there is no biological rationale to assume different outcomes with calaspargase pegol.
- pERC noted that the frequency of AEs appeared to be overall similar between the treatment groups in the DFCI 11-001 trial; however, the safety results in the COG AALL07P4 trial were suggestive of more patients in the calaspargase pegol group experiencing hypoalbuminemia and hyperglycemia than in the pegaspargase group. pERC acknowledged input from the clinical experts noting that because asparaginase was given as part of a MAC protocol it is challenging to attribute differences

in AEs observed in small numbers of patients to a specific component of a multidrug regimen. pERC discussed that the management of toxicity in clinical practice may need adaptation to account for calaspargase pegol's longer half-life compared to pegaspargase.

- pERC discussed the importance of therapeutic drug monitoring in the management of patients treated with asparaginase as a reliable assessment of asparaginase efficacy. The monitoring of SAA levels is used to initiate and monitor response throughout treatment regimens, as well as to distinguish between hypersensitivity due to an allergic reaction, silent inactivation, and other types of asparaginase reactions that do not result in inactivation. However, pERC acknowledged that the routine use of therapeutic drug monitoring might not always be available or feasible in different settings across Canada, resulting in inconsistent use in clinical practice.

Background

ALL is the most common type of leukemia diagnosed in young children. It is estimated that ALL represents 75% to 80% of acute leukemias among children. ALL is the least common type of leukemia diagnosed in adults, representing an estimated 20% of all adult leukemias. In 2018, the incidence rate of ALL for all ages in Canada (excluding Quebec) was 1.3 per 100,000, with the majority of patients being under the age of 19 years. ALL is a heterogeneous group of disorders that result from the clonal proliferation and expansion of malignant lymphoid cells in the bone marrow, blood, and other organs, classified into 2 major subtypes (i.e., B-lymphoblastic and T-lymphoblastic leukemia), with further division according to the presence and type of genetic abnormalities. ALL of the B-cell phenotypes occurs in approximately 80% to 85% of pediatric patients and nearly 75% of adults. The frequency of Ph positive disease in patients with ALL is about 3% to 5% among pediatric patients, and 25% to 30% among adults. The signs and symptoms of ALL are highly variable, with most patients experiencing bruising, bleeding, dyspnea, dizziness, infections due to neutropenia, anemia, thrombocytopenia, and pain. The goal of treatment is curative and comprises MAC regimens that incorporate asparaginase therapy as established standard of care. Two different childhood ALL treatment strategies are commonly used across Canada, originating from the COG and the DFCI consortia; both protocols currently include pegaspargase. According to the clinical experts consulted by CADTH, patients who are unable to receive asparaginase treatment (e.g., they lack access to a consistent supply of the treatment drug or experience intolerance) are less likely to be cured with chemotherapy alone.

The mechanism of action of calaspargase pegol is the same as that of the established standard of care, pegaspargase. To mitigate the risk of drug shortages, the sponsor developed calaspargase pegol to extend the shelf life and half-life relative to the sponsor's original pegaspargase product. Calaspargase pegol and pegaspargase both contain the same asparagine-specific enzyme derived from *E. coli*, as a conjugate of L-asparaginase linked to a similar monomethoxy polyethylene glycol. The only difference between the 2 products is the linker connecting the 2 components. Pegaspargase contains a succinimidyl succinate linker, while calaspargase pegol contains a succinimidyl carbonate linker, the latter being less prone to enzymatic hydrolysis and more stable. As a result of the improved stability, calaspargase pegol has a 36-month shelf life compared to 8 months for the pegaspargase formulation.

Calaspargase pegol has received Health Canada authorization for the treatment of patients with ALL in pediatric and young adult patients age 1 to 21 years. It is available as an IV infusion and the dosage recommended in the draft product monograph is 2,500 units/m^2 given no more frequently than every 21 days as a component of a MAC regimen.

Sources of Information Used by the Committee

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

- a review of 1 randomized controlled trial (RCT) in patients aged 1 year to 30 years with newly diagnosed high-risk B-cell ALL, and 1 RCT in patients aged 1 year to 21 years with newly diagnosed ALL or lymphoblastic lymphoma
- patients' perspectives gathered by 1 patient group, Leukemia & Lymphoma Society of Canada (LLSC)
- input from the public drug plans that participate in the CADTH review process
- input from 2 clinical specialists with expertise diagnosing and treating patients with ALL
- input from 1 clinician group, Ontario Health – Cancer Care Ontario (OH-CCO)
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

Patient Input

CADTH received 1 patient group submission from LLSC. LLSC is a national charitable status organization dedicated to finding a cure for blood cancers and to improve the quality of life of people affected by blood cancers and their families by funding life-enhancing research and providing educational resources, services, and support.

LLSC conducted an online survey with 74 respondents from 10 provinces in Canada during April to May 2023. The majority of respondents (n = 47) identified as patients with ALL and 20 respondents indicated that they were caregivers of patients with ALL. Respondents who indicated that they were neither a patient with ALL nor a caregiver of a patient with ALL were disqualified from the survey. About half of the patients with ALL indicated that they were older than the age of 30 at the time of their ALL diagnosis while the other half was younger than the age of 30.

LLSC stated that the questions in this survey were not intended to measure the efficacy of the drug under review because it was assumed to be as effective as current treatment options and was also budget neutral. The questions in this survey were aimed at highlighting the importance of safeguarding the health care system to ensure that treatment medications are securely supplied for those experiencing ALL.

Survey respondents reported their experience with drug shortage at some point during their ALL treatment. Reponses highlighted extreme stressful conditions, fear treatment will be unsuccessful, feeling powerless

and let down by the system, poor quality of life, and lack of sleep because of stress, anxiety, mood swings, and spending time trying to find an alternative solution. Some respondents noted financial impacts, as they had to pay for alternative therapies and buy products to help them cope.

Respondents indicated that they needed to feel included in decision-making as their treatment plan for ALL would have effects on many areas of their lives. In addition to the effectiveness of the treatment, factors that were important to the patients when evaluating new treatments for ALL included side effects, physician's recommendation, quality of life, cost, secure supply, and number of treatments.

LLSC highlighted that ALL progresses quickly and aggressively and that to prevent disease progression, immediate start of treatment upon diagnosis is vital. Survey respondents expressed that delaying start of treatment may lead to cancer progression, their bodies being less receptive and tolerable to treatment, and potentially death.

LLSC noted the importance of having alternative treatments available to ensure treatment can continue should manufacturers run into supply issues. Having a secure supply of treatment options would provide comfort and peace of mind to patients and their caregivers during an already difficult and challenging time. Most of the survey respondents indicated that they would be supportive of the idea of a government providing public funding for an alternative treatment option for ALL that would work equally well with similar costs to the health care system and would provide treatment assurance in case an alternative ALL medication becomes unavailable.

LLSC asked survey respondents to rate the level of impact treatment shortage due to supply issues would have on their lives. Respondents noted the following areas as being most impacted (listed in order of importance to survey respondents): mental health, physical health, quality of life, home life, social life, work life, and finances.

Respondents were asked by LLSC to describe in 3 words their emotional response to being told that a drug that was part of their treatment regimen was suddenly not available due to supply issues. Survey respondents mostly reported words associated with fear, stress, despair, and defeat.

Clinician Input

Input From Clinical Experts Consulted by CADTH

Two clinical specialists with expertise in the diagnosis and management of ALL reported that the goal of treatment for patients with ALL is curative, aimed at maximizing survival while minimizing short- and long-term toxicities. Current treatment for ALL in Canada was identified by the clinical experts consulted by CADTH to comprise of MAC regimens that include pegylated asparaginase, using pediatric protocols developed by the COG or the DFCI among children or pediatric-inspired protocols among adults. The clinical experts consulted by CADTH noted that patients who do not respond to treatment require high-dose chemotherapy and/or allogeneic stem cell transplant and experience high rates of treatment failure. According to the clinical experts consulted by CADTH, patients would benefit from a consistent supply of asparaginase, with a longer dosing interval, and treatments with improved tolerability.

Asparaginase is an essential component of frontline ALL therapy, and 2 extended half-life formulations have been developed for clinical use. Pegylated asparaginase has a half-life of 5.7 days and is administered every 14 days. Calaspargase pegol has a half-life of 16.1 days and is administered every 21 days. The clinical experts consulted by CADTH did not expect a shift in the current treatment paradigm with calaspargase pegol; rather, they believed that it would replace pegaspargase, given its prolonged half-life, longer dosing interval, and the need for fewer administration over the course of treatment.

The clinical experts consulted by CADTH indicated that all patients with newly diagnosed ALL would benefit from treatment with calaspargase pegol, because asparaginase has a unique mechanism of action and is considered to comprise an essential component of therapy in ALL. Patients with relapsed ALL were also considered by the clinical experts consulted by CADTH to potentially benefit from calaspargase pegol, if there was no known prior intolerance to other forms of asparaginase. Patients of any age, with Ph positive status (except for adults because of potential overlapping toxicities with tyrosine kinase inhibitors), and B-cell or T-cell immunophenotype were considered by the clinical experts consulted by CADTH to be eligible for asparaginase treatment and therefore appropriately targeted for treatment with calaspargase pegol. The clinical experts consulted by CADTH specified that several risk factors are considered before starting treatment to help inform the protocol used, including age older than 10 years, white blood cell (WBC) below 50×10^9/L at presentation or diagnosis, adverse genetic features including karyotype (e.g., translocations (t(9;22)(q34;q11), hypodiploidy), molecular studies (e.g., *BCR-ABL*, *KMT2A* mutations), and gene expression (e.g., IKZF, CRLF2).

The clinical experts consulted by CADTH reported that a clinically meaningful treatment response should be assessed using OS, postinduction CR, postinduction MRD negative status, and SAA levels following administration of asparaginase to monitor adequate asparaginase depletion and clinical reactions (e.g., allergic or infusion-related reaction, silent inactivation). According to the clinical experts consulted by CADTH, treatment with asparaginase, including calaspargase pegol, should be discontinued in the event of notable AEs (e.g., hypersensitivity reaction, including silent inactivation, allergic reaction, development of neutralizing antibodies, severe liver toxicity, severe pancreatitis, severe thrombotic or hemorrhagic event, persistent severe hepatic dysfunction). The clinical experts consulted by CADTH indicated that patients with ALL are often treated in the hospital or cancer centres, as inpatients or outpatients, by hematologists or oncologists.

Clinician Group Input

CADTH received 1 clinician group submission from the OH-CCO Hematology Cancer Drug Advisory Committee comprising 2 clinicians. The clinician group noted no significant unmet need among patients who are eligible for standard induction of ALL treatment with pegaspargase; however, patients treated with calaspargase pegol as a component of MAC may benefit from less frequent dosing and should be assessed for treatment response using standard leukemia response criteria, with treatment to be discontinued upon progressive disease or significant intolerance. OH-CCO noted that the appropriate setting for treatment with calaspargase pegol is an acute leukemia treatment centre with leukemia specialists.

Drug Program Input

Input was obtained from the drug programs that participate in the CADTH reimbursement review process.

The clinical experts consulted by CADTH provided advice on the potential implementation issues raised by the drug programs. Refer to Table 2 for details.

Table 2: Responses to Questions From the Drug Programs

Implementation issues	Response
Relevant comparators	
Two studies, 1 in newly diagnosed ALL or lymphoblastic lymphoma (patients aged 1 to 21 years) and the other in newly diagnosed high-risk B-cell ALL (patients aged 1 to 30 years) compared to pegaspargase. Pegaspargase is funded by several jurisdictions and would be a relevant comparator. Of note, pegaspargase has not been reviewed by CADTH pCODR. Other potentially relevant comparators are crisantaspase and Erwinia-derived asparaginase (Erwinase) — although this is for the setting of hypersensitivity or silent inactivation of the *E-coli*–derived asparaginase. Are there any data for comparators other than pegaspargase?	pERC agreed with the clinical experts consulted by CADTH that pegaspargase is currently used as a component of a multiagent chemotherapy regimen for the treatment for patients with ALL, and therefore considered to be an appropriate comparator for calaspargase pegol. The clinical experts consulted by CADTH were not aware of data or clinical trials to date that use other comparators.
Considerations for initiation of therapy	
The clinical trials were completed in patients under the age of 21 years in the DFCI 11-001 study and under 31 years in the COG AALL07P4 study. 1. Should patients over the age of 21 years be eligible for calaspargase pegol? 2. The clinical trials were completed in patients with newly diagnosed disease. Is there evidence to support use in relapsed or refractory ALL? 3. Should patients with lymphoblastic lymphoma be eligible for calaspargase pegol? 4. Should patients with mixed or biphenotypic leukemia be eligible for calaspargase pegol? 5. Should patients with Ph+ disease, Down syndrome, and T-cell ALL be eligible for calaspargase pegol?	1. Health Canada issued market authorization for calaspargase pegol for the treatment of ALL in pediatric and young adult patients aged 1 to 21 years. The clinical experts agreed that patients younger than 1 or older than 21 are currently treated with asparaginase-based treatment in clinical practice. Given the similar mechanism of action between pegaspargase and calaspargase pegol, pERC agreed with the clinical experts that it would be reasonable to extrapolate the results from the available evidence for calaspargase pegol to patients aged younger than 1 or older than 21. 2. The DFCI 11-001 and COG AALL07P4 trials did not enrol patients with relapsed or refractory ALL. pERC agreed with the clinical experts that calaspargase pegol may also be used for patients with relapsed or refractory ALL, if there was no evidence of prior allergic reaction or hypersensitivity to asparaginase. 3. While the COG AALL07P4 trial excluded patients with lymphoblastic lymphoma; 9 patients with lymphoblastic lymphoma participated in the DFCI 11-001 trial. pERC agreed with the clinical experts that it would be reasonable to generalize the results of the DFCI 11-001 trial to pediatric and young adult patients with LL as they anticipated that treatment outcomes in these patients would be very similar to patients with ALL. 4. The DFCI 11-001 and COG AALL07P4 trials did not enrol patients with mixed or biphenotypic leukemia; however, these patients are currently treated with asparaginase-based treatment in clinical practice. Given the similar mechanism

Implementation issues	Response
	of action between pegaspargase and calaspargase pegol, pERC agreed with the clinical experts that it would be reasonable to extrapolate the results to patients with mixed or biphenotypic leukemia. 5. pERC noted that patients with Ph+ disease were excluded from the available evidence and a minority of patients had Down syndrome and T-cell ALL. pERC agreed with the clinical experts that generalizing the available evidence to patients with T-cell ALL, pediatric patients with Ph+ disease, and patients with Down syndrome may be reasonable.
Considerations for prescribing of therapy	
According to the US product monograph, the standard dose of calaspargase pegol is 2,500 IU/m^2 in 100 mL normal saline/dextrose 5% in water IV over 1 hour every 21 days. It comes as a 3,750 IU single use vial, which means that for patients taller than 1.5 m^2, there will be wastage. However, this is the same dose and vial size as pegaspargase, which is given every 14 days, so there is an advantage to the calaspargase pegol in terms of number of infusions as well as wastage to prepare those doses. In some protocols, pegaspargase is capped at 3,750 IU as a maximum dose. 1. Would capping also apply to calaspargase pegol? 2. Can pERC clarify the dosing schedule for calaspargase pegol as there may be differences in the frequency of administration with pegaspargase?	1. The clinical experts noted that capping the dose of asparaginase products (pegaspargase or calaspargase pegol) at 3,750 IU is permitted according to institutional preference and at the discretion of the treating clinician. The clinical experts reported that the difference in dosing schedule for calaspargase pegol compared to pegaspargase is less notable for COG-based protocols, which use a discontinuous asparaginase depletion strategy, than for DFCI-based protocols, which use a continuous asparaginase depletion strategy. pERC agreed with the clinical experts. pERC noted that monitoring of SAA levels may inform decisions on dose capping. 2. DFCI protocols employ a prolonged intensification phase aimed at continuous asparagine depletion within multiagent chemotherapy. The clinical experts anticipated that for adults who receive calaspargase pegol, the administration schedule for asparaginase would change from an interval of every 14 days (which is used for pegaspargase) to an interval of every 21 days (which is recommended for calaspargase pegol). The clinical experts noted that current COG protocols, unlike DFCI protocols, use a discontinuous asparaginase administration strategy. Thus, current COG protocols do not include repeated every 14-day dosing recommendations for pegaspargase. pERC agreed with the assessment of the clinical experts.
Alignment of the existing funding for pegaspargase would need to be considered (e.g., some jurisdictions fund pegaspargase on a per vial basis and also fund inpatient use).	Comment from the drug programs to inform pERC deliberations.
Generalizability	
Should there be any consideration for switching patients receiving pegaspargase to calaspargase pegol?	The clinical experts consulted by CADTH did not anticipate any issues switching patients who were receiving pegaspargase to calaspargase pegol as the asparaginase component is the same for both drugs. pERC agreed with the clinical experts that patients could be switched from pegaspargase to calaspargase pegol depending on availability. pERC also agreed with the clinical experts that they would not switch patients from pegaspargase to calaspargase pegol for toxicity or inactivation.

Implementation issues	Response
Care provision issues	
Pegaspargase may be given by intramuscular or IV route of administration. Calaspargase pegol is only indicated for IV administration. According to the US product monograph, patients should be monitored for hypersensitivity for 1 hour after administration. The product is stored in the refrigerator; therefore, sufficient fridge space is required.	Comment from the drug programs to inform pERC deliberations.
System and economic issues	
Consideration for pricing should include the usual cost-effectiveness analyses, but also should not exceed the per-cycle drug program cost of treatment with the least costly comparator reimbursed.	Comment from the drug programs to inform pERC deliberations.
There tend to be ongoing shortages of asparaginase products and having alternatives is helpful. Will pegaspargase be available once calaspargase pegol is approved by Health Canada (i.e., will both products be available)?	pERC and the clinical experts noted that they were unable to comment. The sponsor has noted in submission materials received by CADTH for this review, that "…North American COG and DFCI consortia are currently transitioning and amending existing protocols to include calaspargase pegol, as a replacement to pegaspargase.… Following regulatory approval of calaspargase pegol by Health Canada, Servier will also be transitioning to calaspargase pegol in the near future, to securely provide a more reliable supply of a high-quality standard pegylated *E. coli*–derived asparaginase."

ALL = acute lymphoblastic leukemia; COG = Children's Oncology Group; DFCI = Dana-Farber Cancer Institute; LL = lymphoblastic lymphoma; pCODR = CADTH pan-Canadian Oncology Drug; Review pERC = CADTH pan-Canadian Oncology Drug Review Expert Review Committee; Ph+ = Philadelphia chromosome-positive; SAA = serum asparaginase activity.

Clinical Evidence

Systematic Review

Description of Studies

Two phase II, multicentre, randomized, open-label trials assessed the efficacy and safety of calaspargase pegol 2,500 IU/m^2 compared with pegaspargase 2,500 IU/m^2. The COG AALL07P4 trial enrolled 166 patients aged 1 year to 30 years in 23 study sites, all located in the US, with newly diagnosed high-risk B-cell ALL. The primary objective of the COG AALL07P4 trial was to determine the pharmacokinetic (PK) comparability (asparaginase activity) of the interventions during induction and consolidation while patients were receiving augmented Berlin-Frankfurt-Münster chemotherapy. Secondary end points of the COG AALL07P4 trial included pharmacodynamic (PD) parameters during induction and consolidation, MRD (day 29), CR rate (day 29), survival (event-free survival [EFS], disease-free survival [DFS] of CR, and OS), and treatment-emergent events (TEAEs). The DFCI 11-001 trial enrolled 239 patients aged 1 year to 21 years in the US (6 sites) and Canada (3 sites) with newly diagnosed ALL or lymphoblastic lymphoma. The primary objective of the DFCI

11-001 trial was to determine the PK comparability of the interventions during remission induction and postinduction (i.e., determine SAA levels, and assessment of harms). The secondary end points of the DFCI 11-001 trial included MRD (day 32), CR rate (day 32), EFS, DFS of CR, and OS.

Across both the COG AALL07P4 and DFCI 11-001 trials, there were notable similarities and differences in baseline demographics. In the COG AALL07P4 trial, most patients were older than 10 years of age (66.3%). In the DFCI 11-001 trial, most patients were younger than 10 years of age (75%). All patients in the COG AALL07P4 trial and nearly all patients (96%) in the DFCI 11-001 trial had ALL. Most patients in the DFCI 11-001 trial had B-cell ALL (87%), including a minority of patients with T-cell ALL. Patients with B-cell immunophenotype were exclusively enrolled in the COG AALL07P4 trial. Most patients had a central nervous system status of 1 in both trials with a minority of patients designated as central nervous system status 3 in the COG AALL07P4 (fewer than 10% of patients) and DFCI 11-001 (fewer than 2% of patients) trials. Most patients did not have steroid therapy before study treatment in the COG AALL07P4 ([redacted] of patients) or DFCI 11-001 ([redacted] of patients) trials. While the majority of patients were older than 10 years of age in the COG AALL07P4 trial (median 11 years old), most patients were younger than 10 years of age in the DFCI 11-001 trial (median 5.2 years old). Approximately 62% of patients were diagnosed when they were 10 years or older in the COG AALL07P4 trial, whereas nearly 75% of patients were diagnosed below 10 years of age in the DFCI 11-001 trial. Patients in the COG AALL07P4 trial were distributed equally across combined age and WBC categories, whereas more than 70% of patients in the DFCI 11-001 trial were below 10 years of age with a WBC count below 50 × 10^9/L.

Efficacy Results

Results in the COG AALL07P4 trial were based on the December 31, 2015, data cut-off date. Results in the DFCI 11-001 trial were based on the October 5, 2016, data cut-off date, and where indicated, from a day 120 follow-up with an updated data cut-off date of June 12, 2017.

Overall Survival

In the COG AALL07P4 trial, median OS was not reached at the data cut-off on December 31, 2015. Patients had been followed for a median of 62.6 months (range = [redacted]). The 1-year OS rate (95% confidence interval [CI]) among patients in the full analysis set (FAS) population was [redacted] and [redacted] in the calaspargase pegol and pegaspargase group, respectively. The 4-year OS rate (95% CI) among patients in the FAS population was [redacted] in the calaspargase pegol group and [redacted] in the pegaspargase group. The hazard ratio (HR) (95% CI) in the FAS population was [redacted] in the calaspargase pegol versus pegaspargase group. The findings of the intention-to-treat (ITT) population were consistent with the results for the FAS population.

In the DFCI 11-001 trial, median OS was not reached at the data cut-off on October 5, 2016. Patients had been followed for a median of [redacted] months (range = [redacted]). The 1-year OS rate (95% CI) among patients in the FAS ALL population was [redacted] for calaspargase pegol and [redacted] for pegaspargase. At the day 120 cut-off, the median follow-up duration was [redacted] months and [redacted] months for the calaspargase pegol and pegaspargase groups, respectively. The 2-year OS rate (95% CI) among patients in the FAS ALL population

was [redacted] for calaspargase pegol and [redacted] for pegaspargase. The findings of the ITT ALL population were consistent with the results for the FAS population.

DFS From CR

In the COG AALL07P4 trial, the 1-year DFS rate (95% CI) among patients in the FAS population was [redacted] and [redacted] in the calaspargase pegol and pegaspargase groups, respectively. The 4-year DFS rate (95% CI) among patients in the FAS population was [redacted] and [redacted] in the calaspargase pegol and pegaspargase groups, respectively. The HR (95% CI) was [redacted] in the calaspargase pegol group versus pegaspargase. The DFS results in the ITT population were identical to the FAS population.

In the DFCI 11-001 trial, the 1-year DFS rate (95% CI) among patients in the FAS ALL population who achieved CR was [redacted] in the calaspargase pegol group and [redacted] in the pegaspargase group. At day 120 follow-up, the 2-year DFS rate (95% CI) among patients in the FAS ALL population who achieved CR was [redacted] and [redacted] for calaspargase pegol versus pegaspargase, respectively. The DFS results among patients achieving CR in the ITT ALL population were identical to the FAS ALL population.

Event-Free Survival

In the COG AALL07P4 trial, the 1-year EFS rates (95% CI) among patients in the FAS population was [redacted] and [redacted] in the calaspargase pegol and pegaspargase groups, respectively. The 4-year EFS rate (95% CI) was [redacted] and [redacted] in the calaspargase pegol and pegaspargase groups, respectively. The HR (95% CI) was [redacted] for calaspargase pegol when compared with pegaspargase. The findings for EFS in the ITT population were consistent with the results for the FAS population.

In the DFCI 11-001 trial, the 1-year EFS rate (95% CI) among patients in the FAS ALL population was [redacted] and [redacted] in the calaspargase pegol and pegaspargase groups, respectively. At day 120 follow-up, the 2-year EFS rate (95% CI) at the 120 update was [redacted] and 98.0% [redacted] in the calaspargase pegol and pegaspargase groups, respectively. The EFS results among patients in the ITT ALL population were consistent with the results for the FAS ALL population.

Complete Remission

In the COG AALL07P4 trial, the proportion of patients in the FAS population who achieved CR (95% CI) by day 29 was [redacted] in the calaspargase pegol group and [redacted] in the pegaspargase group. Findings for CR at the end of induction day 29 for the ITT population were consistent with the results for the FAS population.

In the DFCI 11-001 trial, the proportion of patients in the FAS ALL population who achieved CR (95% CI) by day 32 was [redacted] in the calaspargase pegol group and [redacted] in the pegaspargase group. Results for CR by day 32 in the ITT ALL population were consistent with the results for the FAS ALL population.

Minimal Residual Disease

In the COG AALL07P4 trial, the proportion of patients in the MRD-evaluable ITT population with positive MRD (≥ 0.1% detectable leukemia cells in bone marrow biopsy or aspirate with validated 6-colour multiparameter flow cytometry) at induction day 29 was [redacted] in the calaspargase pegol and [redacted] in the pegaspargase group.

The findings for positive MRD (≥ 0.1%) at the end of induction day 29 in the ITT population were consistent with the results in the FAS population.

In the DFCI 11-001 trial, the proportion of patients in the FAS ALL population with an MRD of 0.01 or greater was [redacted] in the calaspargase pegol group and [redacted] in the pegaspargase group. The findings for an MRD of 0.01 or greater at the end of induction day 32 in the ITT ALL population were consistent with the results in the FAS ALL population.

Serum Asparaginase Activity

SAA levels were not reported in the COG AALL07P4 trial.

In the DFCI 11-001 trial, the proportion of patients with SAA levels of 0.10 IU/mL or greater (95% CI) was [redacted] for calaspargase pegol versus [redacted] for pegaspargase at 5 minutes to 10 minutes after infusion on induction day 7 (odds ratio [OR] = [redacted]; 90% CI, [redacted]). The proportion of patients with SAA levels of 0.10 IU/mL or greater was [redacted] (95% CI, [redacted]) for calaspargase pegol versus [redacted] (95% CI, [redacted]) for pegaspargase at 4 days after infusion on day 11 (OR = [redacted]; 90% CI, [redacted]). The proportion of patients with SAA levels of 0.10 IU/mL or greater (95% CI) was [redacted] for calaspargase pegol versus [redacted] for pegaspargase at 11 days after infusion on day 18 (OR = [redacted]; 90% CI, [redacted]). The proportion of patients with SAA levels of 0.10 IU/mL or greater (95% CI) was [redacted] for calaspargase pegol versus [redacted] for pegaspargase at 18 days after infusion on day 25 (OR = [redacted]; 90% CI, [redacted]). The proportion of patients with SAA levels of 0.10 IU/mL or greater (95% CI) was [redacted] for calaspargase pegol versus [redacted] for pegaspargase at 25 days after infusion on day 32 (OR = [redacted]; 90% CI, [redacted]). The estimates of treatment effect on SAA levels using adjusted analyses (controlled for age, sex, initial risk group, disease type, and baseline WBC count) were similar to unadjusted analyses.

Harms Results

The analysis population for harms included all patients who received at least 1 dose of any study drug, with patients grouped according to the treatment received. Safety data were from the primary safety analyses for the COG AALL07P4 (data cut-off date of December 31, 2015) and DFCI 11-001 (data cut-off date of October 5, 2016) trials.

In the COG AALL07P4 trial, the percentage of patients reporting any TEAEs was [redacted] for calaspargase pegol and [redacted] for pegaspargase. In the DFCI 11-001 trial, the percentage of patients who experienced any TEAEs was [redacted] in the calaspargase pegol group and [redacted] in the pegaspargase group. In the COG AALL07P4 trial, the most common TEAEs occurring in at least 25% of patients in either treatment group (calaspargase pegol versus pegaspargase) were hypoalbuminemia (27.9% versus 5.8%), hyperglycemia (79.1% versus 50.0%), increased blood bilirubin (62.8% versus 50.0%), decreased neutrophil count (55.8% versus 51.9%), febrile neutropenia (55.8% versus 42.3%), increased alanine aminotransferase 34.9% versus 38.5%), decreased platelet count (34.9% versus 25.0%), decreased WBC (37.2% versus 28.5%), hypokalemia (27.9% versus 11.5%), anemia (25.6% versus 26.9%), prolonged activated partial thromboplastin time (30.2% versus 19.2%), peripheral motor neuropathy (27.9% versus 19.2%), and abdominal pain (32.6% versus 11.5%). In the DFCI 11-001 trial, the most common TEAEs occurring in at least 25% of patients in either treatment group

(calaspargase pegol versus pegaspargase) were hypoalbuminemia (81.4% versus 82.4%), increased alanine transaminase (78.8% versus 77.3%), increased aspartate aminotransferase (53.4% versus 58.8%), increased blood bilirubin (45.8% versus 43.7%), hypokalemia (45.8% versus 39.5%), febrile neutropenia (33.9% versus 40.3%), hyperglycemia (33.9% versus 28.6%), hypoglycemia (30.5% versus 36.1%), hypertriglyceridemia (28.0% versus 36.1%), and stomatitis (25.4% versus 20.2%).

In the COG AALL07P4 trial, the percentage of patients with at least 1 serious adverse event (SAE) was not reported. The percentage of patients with at least 1 grade 3 or 4 TEAE was 97.7% in the calaspargase pegol group and 90.4% in the pegaspargase group. The most common grade 3 or 4 TEAEs in the calaspargase pegol versus the pegaspargase group were decreased neutrophil count (55.8% versus 51.9%), febrile neutropenia (55.8% versus 42.3%), decreased WBC (37.2% versus 28.8%), and hyperglycemia (37.2% versus 17.3%). In the DFCI 11-001 trial, the percentage of patients who experienced grade 3 or 4 TEAEs was [redacted] in the calaspargase pegol group and [redacted] in the pegaspargase group. The most common grade 3 or 4 TEAEs in the calaspargase pegol versus the pegaspargase group were increased alanine aminotransferase (49.2% versus 60.5%), hypokalemia (43.2% versus 36.1%), febrile neutropenia (33.9% versus 40.3%), and hypoalbuminemia (27.1% versus 27.7%). The percentages of patients who experienced at least 1 SAE were 24.6% and 21.8% in the calaspargase pegol and pegaspargase groups, respectively. SAEs that occurred in at least 2% of patients in the calaspargase pegol versus the pegaspargase group were increased lipase (4.2% versus [redacted]), pancreatitis (5.9% versus [redacted]), sepsis (3.4% versus [redacted]), hyperglycemia (2.5% versus [redacted]), febrile neutropenia (1.7% versus [redacted]), increased amylase (0.8% versus [redacted]), increased alanine aminotransferase (2.5% versus [redacted]), increased aspartate aminotransferase (2.5% versus |), and neutropenic colitis (2.5% versus |).

In the COG AALL07P4 trial, the percentage of patients who stopped study treatment due to an AE were [redacted] and [redacted] in the calaspargase pegol and pegaspargase group, respectively. Reasons for stopping study treatment due to an AE were not reported. In the DFCI 11-001 trial, the percentage of patients who stopped study treatment due to an AE were 28.0% in the calaspargase pegol group and 19.3% in the pegaspargase group. Withdrawals due to AEs in the calaspargase pegol group versus the pegaspargase were due to hypersensitivity (8.5% versus [redacted]), increased lipase (6.8% versus [redacted]), pancreatitis (5.9% [redacted]), drug hypersensitivity (5.1% versus [redacted]), increased amylase (4.2% versus [redacted]), and anaphylactic reaction (1.7% versus [redacted]).

[redacted]

Notable harms identified in the CADTH review included hypersensitivity reactions, anaphylactic reactions, silent inactivation, pancreatitis, thrombosis, hemorrhage, and hepatotoxicity. In the COG AALL07P4 trial, [redacted] of patients in the calaspargase pegol group and [redacted] of patients in the pegaspargase group experienced hypersensitivity events. In the DFCI 11-001 trial, [redacted] of patients in the calaspargase pegol group and [redacted] of patients in the pegaspargase group experienced hypersensitivity events. In the COG AALL07P4 trial, 25.6% of patients in the calaspargase pegol group and 19.2% of patients in the pegaspargase group experienced anaphylactic reactions. In the DFCI 11-001 trial, [redacted] of patients in each treatment group experienced

anaphylactic reactions. In the COG AALL07P4 trial, silent inactivation was not reported by any patient. In the DFCI 11-001 trial, 1.7% of patients in the calaspargase pegol group experienced silent inactivation and were switched to Erwinia asparaginase treatment. In the COG AALL07P4 trial, 18.6% and 7.7% of patients experienced pancreatitis in the calaspargase pegol and pegaspargase groups, respectively. In the DFCI 11-001 trial, 11.9% and 16.8% of patients experienced pancreatitis in the calaspargase pegol and pegaspargase groups, respectively. In the COG AALL07P4 trial, venous thrombosis was [redacted]. In the DFCI 11-001 trial, [redacted] of patients experienced venous thrombosis in each of the calaspargase pegol and pegaspargase groups. [redacted] experienced hemorrhage in the COG AALL07P4 or DFCI 11-001 trials. In the COG AALL07P4 trial the percentage of patients who experienced increased blood bilirubin was 62.8% and 50.0%; the percentage of patients who experienced increased alanine aminotransferase was 34.9% and 38.5% in the calaspargase pegol and pegaspargase groups, respectively. In the DFCI 11-001 trial, the percentage of patients who experienced increased blood bilirubin was 45.8% and 43.7%, and for increased alanine aminotransferase was 78.8% and 77.3% in the calaspargase pegol and pegaspargase groups, respectively. [redacted] in the calaspargase pegol group experienced hepatic failure.

Critical Appraisal

The COG AALL07P4 and DFCI 11-001 trials were phase II, randomized, open-label RCTs. Randomization appeared to be adequate in the COG AALL07P4 and DFCI 11-001 trials because the treatment groups were generally balanced for key baseline characteristics and therefore likely to be at low risk for selection bias. The open-label study design may have biased outcomes with subjective assessments for harms due to knowledge of assigned treatment, although the direction for potential bias is unclear. The COG AALL07P4 and DFCI 11-001 trials were not designed to assess comparative efficacy between calaspargase pegol and pegaspargase. The sample sizes (N = 97 in the COG AALL07P4 trial and N = 239 in the DFCI 11-001 trial) were relatively small and the magnitude of the treatment effect estimates observed in a small study sample may not be replicable in a larger study sample. The findings from the COG AALL07P4 and DFCI 11-001 trials were not controlled for multiple comparisons. There were balanced between-group proportions of patients who were censored or had missing outcomes data that was unlikely to substantially impact findings in the COG ALL07P4 or DFCI 11-001 trials despite lack of imputation. Differences in trial population and backbone treatment protocols in the COG AALL07P4 and DFCI 11-001 trials precluded the ability to combine findings across outcomes. In the COG AALL07P4 and DFCI 11-001 trials, median survival estimates were not reached at the time of data cut-off. Assessments for CR and MRD at day 29 appeared to be appropriate to capture the presence or absence of disease at the end of remission induction. SAA levels were a primary end point in the DFCI 11-001 trial and have been reported to serve as an important end point in assessing calaspargase pegol's ability to maintain asparagine suppression in the plasma, its half-life duration, and its ability to be administered with a lower dosing frequency than pegaspargase. HRQoL was not assessed in either of the 2 trials. The comparator used in the COG AALL07P4 and DFCI 11-001 trials was appropriate as pegaspargase is a pegylated formulation of asparaginase (calaspargase pegol uses the same mechanism of action as pegaspargase) and is a component of current standard of care. Calaspargase pegol is intended to substitute pegaspargase and would be used for patients who would otherwise receive a pegaspargase-containing MAC.

The COG AALL07P4 and DFCI 11-001 trials were phase II trials and enrolled small samples of patients with ALL. The clinical experts consulted by CADTH remarked that small patient populations are expected given the disease area and a phase III RCT would likely neither be feasible nor ethical to conduct. While patients in the COG AALL07P4 and DFCI 11-001 trials were considered representative of patients with ALL, the subpopulations of patients excluded from enrolment included pediatric patients with Ph positive status (excluded from the COG AALL07P4 and DFCI 11-001 trials), patients with T-cell immunophenotype (excluded from the COG AALL07P4 trial), and patients with relapsed or refractory disease (excluded from the COG AALL07P4 and DFCI 11-001 trials). According to the clinical experts consulted by CADTH, the effects of treatment with calaspargase pegol could be generalizable to these patients. The clinical experts consulted by CADTH noted that it is anticipated that patients would benefit from treatment with calaspargase pegol based on its similarity to pegaspargase, as well as the extrapolation of the findings for pegaspargase. Different backbone therapies were employed, with an intermittent versus continuous asparagine depletion protocol for the COG AALL07P4 versus DFCI 11-001 trials, respectively. The clinical experts consulted by CADTH observed both the COG-based and DFCI-based protocols to be employed by institutions across Canada. The clinical experts consulted by CADTH expected outcomes to be similar regardless of the treatment protocol employed for patients with ALL. The outcomes reported in the COG AALL07P4 and DFCI 11-001 trials appeared to be aligned with the outcomes of interest for patients with ALL according to the clinical experts consulted by CADTH. The clinical experts consulted by CADTH highlighted the importance of SAA levels in therapeutic drug monitoring for both efficacy (i.e., adequate asparagine depletion and sustained SAA levels of 0.10 IU/mL or greater) and safety (e.g., hypersensitivity reactions including silent inactivation). In general, the clinical experts consulted by CADTH did not anticipate clinically meaningful differences in efficacy between calaspargase pegol and pegaspargase.

Long-Term Extension Studies

No long-term extension studies were submitted in the systematic review evidence.

Indirect Comparisons

No indirect treatment comparisons were submitted in the systematic review evidence.

Studies Addressing Gaps in the Evidence From the Systematic Review

No additional studies addressing important gaps in the systematic review evidence were identified.

GRADE Summary of Findings and Certainty of the Evidence

Methods for Assessing the Certainty of the Evidence

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

The selection of outcomes for GRADE assessment was based on the sponsor's Summary of Clinical Evidence, consultation with clinical experts, and input received from patient and clinician groups and public drug plans. The following list of outcomes was finalized in consultation with expert committee members: survival (OS, DFS, and EFS), CR at the end of induction, MRD at the end of induction, SAA levels, and harms (withdrawal due to AEs, hypersensitivity reactions, anaphylactic reactions, and silent inactivation).

When possible, certainty was rated in the context of the presence of an important (nontrivial) treatment effect; if this was not possible, certainty was rated in the context of the presence of any treatment effect (i.e., the clinical importance is unclear). In all cases, the target of the certainty of evidence assessment was based on the point estimate and where it was located relative to the threshold for a clinically important effect (when a threshold was available) or to the null. The target of the certainty of evidence assessment was the presence or absence of a clinically important effect for CR at the end of induction based on a threshold informed by the clinical experts consulted by CADTH for this review. The target of the certainty of evidence assessment was the presence or absence of any (non-null) effect for survival rates (OS, DFS from CR, EFS), MRD at the end of induction, SAA during induction, and harms.

For the GRADE assessments, findings from the COG AALL07P4 and DFCI 11-001 trials were assessed individually because the trials were different in terms of enrolled populations (patients with high-risk B-cell ALL in the COG AALL07P4 trial and patients with ALL and lymphoblastic lymphoma in the DFCI 11-001 trial) and employed different treatment protocols (intermittent asparagine depletion in the COG AALL07P4 trial and continuous asparagine depletion in the DFCI 11-001 trial).

Table 3: Summary of Findings for Calaspargase Pegol Versus Pegaspargase for Patients With High-Risk B-cell Acute Lymphoblastic Leukemia in the COG AALL07P4 Trial

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Pegaspargase 2,500 IU/m²	Calaspargase pegol 2,500 IU/m²	Difference		
Overall survival — full analysis set							
Probability of being alive at 1 year Median follow-up: 62.6 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Low[a]	Calaspargase pegol may result in little to no difference in overall survival at 1 year when compared with pegaspargase. There is some uncertainty about the clinical importance of the estimates.
Probability of being alive at 4 years Median follow-up: 62.6 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Low[a]	Calaspargase pegol may result in little to no difference in overall survival at 4 years when compared with pegaspargase. There is some uncertainty in the clinical importance of the estimates.
Disease-free survival from complete remission — full analysis set							
Probability of being alive and disease-free from complete remission at 1 year Median follow-up: 62.6 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Low[b]	Calaspargase pegol may result in little to no difference in disease-free survival from complete remission at 1 year when compared with pegaspargase. There is some uncertainty in the clinical importance of the estimates.
Probability of being alive and disease-free from complete remission at 4 years Median follow-up: 62.6 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Moderate[c]	Calaspargase pegol likely results in little to no difference in disease-free survival from complete remission at 4 years when compared with pegaspargase. There is some uncertainty in the clinical importance of the estimates.

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Pegaspargase 2,500 IU/m^2	Calaspargase pegol 2,500 IU/m^2	Difference		
Event-free survival — full analysis set							
Probability of being alive and event-free at 1 year Median follow-up: 62.6 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Low[a]	Calaspargase pegol may result in little to no difference in event-free survival at 1 year when compared with pegaspargase. There is some uncertainty in the clinical importance of the estimates.
Probability of being alive and event-free at 4 years Median follow-up: 62.6 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Low[a]	Calaspargase pegol may result in little to no difference in event-free survival at 4 years when compared with pegaspargase. There is some uncertainty in the clinical importance of the estimates.
Complete remission at end of induction day 29 — full analysis set							
Complete remission rate at end of induction Follow-up: day 29	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Low[d]	Calaspargase pegol may result in an increase in complete remission at the end of induction day 29 when compared with pegaspargase.
Minimal residual disease (positive MRD, ≥ 0.1%) at end of induction day 29 — full analysis set							
Positive minimal residual disease (≥ 0.1%) rate at end of induction Follow-up: day 29	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Low[a]	Calaspargase pegol may result in little to no difference in positive minimal residual disease (≥ 0.1%) at the end of induction day 29 when compared with pegaspargase. There is some uncertainty in the clinical importance of the estimates.

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Pegaspargase 2,500 IU/m^2	Calaspargase pegol 2,500 IU/m^2	Difference		
Serum asparaginase activity ≥ 0.10 IU/mL during remission induction							
Serum asparaginase activity ≥ 0.10 IU/mL rate	NA	No data available	No data available	No data available	No data available	NA	There is no evidence for the effect of calaspargase pegol on serum asparaginase activity when compared with pegaspargase.
HRQoL							
HRQoL due to treatment	NA	No data available	No data available	No data available	No data available	NA	There is no evidence for the effect of calaspargase pegol on HRQoL when compared with pegaspargase.
Harms — safety analysis set							
Withdrawals due to adverse events Follow-up: throughout study	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Very low[e,f]	The evidence is very uncertain about the effects on withdrawals due to adverse events of calaspargase pegol when compared with pegaspargase. There is some uncertainty in the clinical importance of the estimates.
Hypersensitivity reactions Follow-up: throughout study	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Low[f]	Calaspargase pegol may result in little to no difference in hypersensitivity reactions when compared with pegaspargase. There is some uncertainty in the clinical importance of the estimates.
Anaphylactic reactions Follow-up: throughout study	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Low[f]	Calaspargase pegol may result in little to no difference in anaphylactic reactions when compared with pegaspargase. There is some uncertainty in the clinical importance of the estimates.

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Pegaspargase 2,500 IU/m^2	Calaspargase pegol 2,500 IU/m^2	Difference		
Silent inactivation Follow-up: throughout study	NA	No data available	No data available	No data available	No data available	NA	There is no evidence for the effect of calaspargase pegol on silent inactivation when compared with pegaspargase.

COG = Children's Oncology Group; CI = confidence interval; HRQoL = health-related quality of life; NA = not applicable.

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

[a]Rated down 2 levels for very serious imprecision. There is no established minimal important difference and the clinical experts consulted by CADTH could not provide a threshold of important difference. In the absence of a known threshold, the null was used. The CADTH review team judged the point estimate for the between-group difference unlikely to include an important effect; however, the upper and lower bounds of the 95% CI for difference between groups suggested a possibility of both benefit and harm.

[b]Rated down 2 levels for very serious imprecision. No threshold was identified in the literature, but according to the clinical experts consulted by CADTH for the review, any difference in disease-free survival could be considered clinically meaningful, so the null was used as the threshold. The CADTH review team judged the point estimate for the between-group difference unlikely to include an important effect; however, the upper and lower bounds of the 95% CI for difference between groups suggested a possibility of both benefit and harm.

[c]Rated down 1 level for serious imprecision. No threshold was identified in the literature, but according to the clinical experts consulted by CADTH for the review, any difference in disease-free survival could be considered important, so the null was used as the threshold. The CADTH review team judged the effect estimate unlikely to include any important effect; however, the upper bound of the 95% CI for difference between groups suggested a possibility of benefit.

[d]Rated down 2 levels for very serious imprecision. No threshold was identified in the literature, but according to the clinical experts consulted by CADTH for the review, a 5% difference between groups in complete remission could be considered clinically meaningful; however, the upper and lower bounds of the 95% CI for difference between groups suggested a possibility of both important benefit and important harm.

[e]Rated down 1 level for risk of bias. The open-label study design may have biased withdrawals due to adverse events from patients' and assessors' knowledge of assigned treatment, although the direction of the potential bias is unclear. Moreover, the clinical experts consulted by CADTH noted that because asparaginase is given as part of a multiagent chemotherapy protocol, it is challenging to attribute differences in adverse events observed in small numbers of patients to a single treatment protocol component.

[f]Rated down 2 levels for very serious imprecision. In the absence of an established threshold, the null was used. The CADTH review team judged the point estimate for the between-group difference unlikely to include an important effect; however, the effect estimate was based on very few events. Moreover, the clinical experts consulted by CADTH noted that because asparaginase is given as part of a multiagent chemotherapy protocol, it is challenging to attribute differences in adverse events observed in small numbers of patients to a single treatment protocol component.

Source: COG AALL07P4 Clinical Study Report. The details included in the table were provided from the sponsor in response to a request for additional data.

Table 4: Summary of Findings for Calaspargase Pegol Versus Pegaspargase for Patients With Acute Lymphoblastic Leukemia in the DFCI 11-001 Trial

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Pegaspargase	Calaspargase pegol	Difference		
Overall survival — full analysis set							
Probability of being alive at 1 year Median follow-up: 26.6 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Moderate[a]	Calaspargase pegol likely results in little to no difference in overall survival at 1 year when compared with pegaspargase. There is some uncertainty in the clinical importance of the estimates.
Probability of being alive at 2 years Median follow-up: 26.6 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Low[b]	Calaspargase pegol may result in little to no difference in overall survival at 2 years when compared with pegaspargase. There is some uncertainty about the clinical importance of the estimates.
Disease-free survival from complete remission — full analysis set							
Probability of being alive and disease-free from complete remission at 1 year Median follow-up: 26.6 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Low[c]	Calaspargase pegol may result in little to no difference in disease-free survival from complete remission at 1 year when compared with pegaspargase. There is some uncertainty about the clinical importance of the estimates.
Probability of being alive and disease-free from complete remission at 2 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Moderate[d]	Calaspargase pegol likely results in little to no difference in disease-free survival at 2 years

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Pegaspargase	Calaspargase pegol	Difference		
Median follow-up: 26.6 months							when compared with pegaspargase. There is some uncertainty in the clinical importance of the estimates.
Event-free survival — full analysis set							
Probability of being alive and event-free at 1 year Median follow-up: 26.6 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Low[e]	Calaspargase may result in little to no difference in event-free survival at 1 year when compared with pegaspargase. There is some uncertainty about the clinical importance of the estimates.
Probability of being alive and event-free at 2 years Median follow-up: 26.6 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Moderate[a]	Calaspargase likely results in little to no difference in event-free survival at 2 years when compared with pegaspargase. There is some uncertainty in the clinical importance of the estimates.
Complete remission at end of induction — full analysis set							
Complete remission rate at end of induction Follow-up: day 32	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Moderate[f]	Calaspargase pegol likely results in little to no difference in complete remission at the end of induction day 32 when compared with pegaspargase.
Minimal residual disease (≥ 0.01) at end of induction — full analysis set							
Minimal residual disease ≥ 0.01 rate Follow-up: day 32	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Low[b]	Calaspargase pegol may result in little to no difference in minimal

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Pegaspargase	Calaspargase pegol	Difference		
							residual disease (≥ 0.01) at the end of induction day 32 when compared with pegaspargase. There is some uncertainty about the clinical importance of the estimates.
Serum asparaginase activity ≥ 0.10 IU/mL during remission induction — pharmacokinetic analysis set							
Serum asparaginase activity ≥ 0.10 IU/mL rate Follow-up: day 7 (4 minute to 5 minute postinfusion)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Low[h]	Calaspargase pegol may result in little to no difference in SAA ≥ 0.10 IU/mL 4 minutes to 5 minutes postinfusion when compared with pegaspargase. There is some uncertainty about the clinical importance of the estimates.
Serum asparaginase activity ≥ 0.10 IU/mL rate Follow-up: day 11 (4 days after dose)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Low[h]	Calaspargase pegol may result in little to no difference in SAA ≥ 0.10 IU/mL 4 days postinfusion when compared with pegaspargase. There is some uncertainty about the clinical importance of the estimates.
Serum asparaginase activity ≥ 0.10 IU/mL rate Follow-up: day 18 (11 days after dose)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Low[h]	Calaspargase pegol may result in little to no difference in SAA ≥ 0.10 IU/mL 11 days postinfusion when compared with pegaspargase. There is some uncertainty about the clinical importance of the estimates.

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Pegaspargase	Calaspargase pegol	Difference		
Serum asparaginase activity ≥ 0.10 IU/mL rate Follow-up: day 25 (18 days after dose)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Moderate[j]	Calaspargase pegol likely results in little to no difference in SAA ≥ 0.10 IU/mL 18 days postinfusion when compared with pegaspargase. There is some uncertainty in the clinical importance of the estimates.
Serum asparaginase activity ≥ 0.10 IU/mL rate Follow-up: day 32 (25 days after dose)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Moderate[j]	Calaspargase pegol likely results in a greater proportion of patients with SAA ≥ 0.10 IU/mL 25 days postinfusion when compared with pegaspargase. There is some uncertainty in the clinical importance of the estimates.
HRQoL							
HRQoL due to treatment	NA	No data available	No data available	No data available	No data available	NA	There is no evidence for the effect of calaspargase pegol on HRQoL when compared with pegaspargase.
Harms — safety analysis set							
Withdrawals due to adverse events Follow-up: throughout study	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Very low[k,l]	The evidence is very uncertain for the effect of calaspargase pegol on withdrawals due to adverse events when compared with pegaspargase. There is some uncertainty in the clinical importance of the estimates.

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Pegaspargase	Calaspargase pegol	Difference		
Hypersensitivity reactions Follow-up: throughout study	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Low[l]	Calaspargase pegol may result in little to no difference in hypersensitivity reactions when compared with pegaspargase. There is some uncertainty about the clinical importance of the estimates.
Anaphylactic reactions Follow-up: throughout study	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Low[l]	Calaspargase pegol may result in little to no difference in anaphylactic reactions when compared with pegaspargase. There is some uncertainty about the clinical importance of the estimates.
Silent inactivation Follow-up: throughout study	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Low[l]	Calaspargase pegol may result in little to no difference in silent inactivation when compared with pegaspargase. There is some uncertainty about the clinical importance of the estimates.

CI = confidence interval; DFCI = Dana-Farber Cancer Institute; HRQoL = health-related quality of life; NA = not applicable; SAA = serum asparaginase activity.

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

[a]Rated down 1 level for serious imprecision. There is no known threshold and the clinical experts consulted by CADTH could not provide a threshold of important difference. In the absence of a known threshold, the null was used. The CADTH review team judged the point estimate for the between-group difference unlikely to include an important effect; however, the lower bound of the 95% CI for the difference between groups suggested a possibility of harm.

[b]Rated down 2 levels for very serious imprecision. In the absence of a known threshold, the CADTH team rated their certainty in a nonzero effect. Although no threshold (i.e., the null) is crossed, the effect estimate is based on very few events in each group.

[c]Rated down 2 levels for very serious imprecision. According to the clinical experts consulted by CADTH for the review, any difference in disease-free survival could be considered clinically meaningful, so the null was used as the threshold. The CADTH review team judged the point estimate for the between-group difference unlikely to include an important effect; however, the effect estimate was based on very few events.

[d]Rated down 1 level for serious imprecision. According to the clinical experts consulted by CADTH for the review, any difference in disease-free survival could be considered clinically meaningful, so the null was used as the threshold. The CADTH review team judged the between-group difference unlikely to include an important effect; however, the lower bound of the 95% CI for the difference between groups suggested a possibility of harm.

[e]Rated down 2 levels for very serious imprecision. There is no established minimal important difference and the clinical experts consulted by CADTH could not provide a threshold of important difference. In the absence of a known threshold, the null was used. The CADTH review team judged the point estimate for the between-group difference unlikely to include an important effect; however, the upper and lower bounds of the 95% CI for difference between groups suggested a possibility of both benefit and harm.

[f]Rated down 1 level for serious imprecision. No known threshold was identified but according to the clinical experts consulted by CADTH for the review, a 5% difference between groups in complete remission could be considered clinically meaningful. The CADTH review team judged the effect estimate unlikely to include an important effect; however, the lower bound of the 95% CI for difference between groups suggested a possibility of important harm.

[g]Odds ratios of SAA levels were estimated using a generalized estimating equation model for comparing categorical SAA levels between treatments, with 90% CIs, adjusted for the following: treatment, actual sampling time points, and interaction of treatment and actual sampling time points as effects.

[h]Rated down 2 levels for very serious imprecision. In the absence of a known threshold, the null was used. The CADTH review team judged the point estimate for the between-group difference unlikely to include an important effect; however, the effect estimate was based on very few events.

[i]Rated down 1 level for serious imprecision. There is no known threshold and the clinical experts consulted by CADTH could not provide a threshold of important difference, so the null was used as the threshold. The CADTH review team judged the point estimate for the between-group difference unlikely to include an important effect; however, the 95% CI for the difference between groups suggested a possibility of benefit.

[j]Rated down 1 level for serious imprecision. There is no known threshold and the clinical experts consulted by CADTH could not provide a threshold of important difference, so the null was used as the threshold. The CADTH team judged the point estimate for the between-group difference likely to include an important benefit. Both lower and upper boundaries of the 95% CI of the between-group difference suggested a possibility of benefit. Although no threshold (i.e., the null) was crossed, the effect estimate was based on relatively few events in each group.

[k]Rated down 1 level for risk of bias due to open-label study design and patients' and assessors' knowledge of assigned treatment. The open-label study design may have biased withdrawals due to adverse events from knowledge of assigned treatment, although the direction of the potential bias is unclear. Moreover, the clinical experts consulted by CADTH noted that because asparaginase is given as part of a multiagent chemotherapy protocol, it is challenging to attribute differences in AEs observed in small numbers of patients to a single treatment protocol component.

[l]Rated down 2 levels for very serious imprecision. In the absence of an established threshold, the null was used. The CADTH review team judged the point estimate for the between-group difference unlikely to include an important effect; however, the effect estimate was based on very few events. Moreover, the clinical experts consulted by CADTH noted that because asparaginase is given as part of a multiagent chemotherapy protocol, it is challenging to attribute differences in adverse events observed in small numbers of patients to a single treatment protocol component.

Source: DFCI 11-001 Clinical Study Report. The details included in the table were provided from the sponsor in response to a request for additional data.

Economic Evidence

Note that the sponsor's application was filed on a pre-Notice of Compliance (NOC) basis and the pharmacoeconomic submission is reflective of the proposed indication and information incorporated in the draft product monograph that was submitted to Health Canada and CADTH. The sponsor's submission included a broader age range than the final indication; however, other details incorporated in the final product monograph were not considered within the review, which suggested the potential for increased resource use associated with calaspargase pegol.

Cost and Cost-Effectiveness

Table 5: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Combination decision tree and PSM
Target population	Patients with ALL receiving an asparaginase-containing MAC regimen
Treatment	Calaspargase pegol as a component of a MAC regimen
Dose regimen	2,500 units per m^2 given by IV no more frequently than every 21 days
Submitted price	$7,441.88 per 3,750 units/5 mL (750 units/mL) vial
Treatment cost	$52,093 per patient, based on a 7-dose course of treatment, per the COG AALL07P4 trial protocol
Comparator	Pegaspargase (Oncaspar)
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (89 years)
Key data sources	The COG AALL07P4 trial The DFCI 11-001 trial
Key limitations	• The comparative clinical efficacy and safety of calaspargase pegol and pegaspargase is uncertain. The CADTH clinical appraisal identified uncertainty in the available clinical evidence because of differences between groups resulting from small sample sizes, wide confidence intervals, and the absence of clinically meaningful thresholds. Despite the uncertainty with the clinical evidence, based on clinical expert feedback obtained by CADTH, and the CADTH appraisal, calaspargase pegol is expected to have little to no difference in OS, DFS, EFS, MRD, hypersensitivity reactions, and anaphylactic reactions compared with pegaspargase. • In the sponsor's submitted economic analysis, patient characteristics were assumed to be comparable with the population in the COG AALL07P4 trial. However, clinical expert feedback obtained by CADTH indicated that the patient population in the COG AALL07P4 trial is not representative pediatric population observed in Canadian clinical practice, and that the DFCI trial population more accurately represents the age of the patient population with ALL at treatment initiation. • The sponsor assumed both calaspargase pegol and pegaspargase treatment would be provided for 38 weeks, although clinical expert feedback indicated that the total duration of MAC treatment for patients with ALL who respond is approximately 2.5 to 3.5 years. If the treatment duration of asparaginase therapies differs, total treatment costs may differ. • Comparator pricing is not publicly available. Pegaspargase acquisition costs were provided by Servier

Component	Description
	Canada and could not be validated by CADTH. CADTH noted that availability of and accessibility to pegaspargase may vary based on jurisdiction. Although the sponsor suggested that calaspargase pegol would only be used for patients who would have otherwise received pegaspargase, CADTH could not address the validity of this assertion. Therefore, it is uncertain if the reimbursement of calaspargase pegol will result in fewer incremental costs than pegaspargase.
CADTH reanalysis results	• CADTH undertook a reanalysis to address limitations, which included assuming equivalent clinical efficacy, assuming equivalent adverse event management costs, and altering characteristics of patients who enter the model to more closely reflect Canadian clinical practice. • Based on the CADTH base case, calaspargase pegol is associated with a higher cost (incremental cost = $4,088) and equal QALYs compared with pegaspargase. • CADTH could not validate the price of pegaspargase paid by CADTH-participating drug plans. As such, the magnitude of the price reduction may be required to ensure no additional costs are incurred is uncertain.

ALL = acute lymphoblastic leukemia; COG = Children's Oncology Group; DCFI = Dana-Farber Cancer Institute; DFS = disease-free survival; EFS = event-free survival; LY = life-year; MAC = multiagent chemotherapeutic; MRD = minimal residual disease; OS = overall survival; PSM = partitioned survival model; QALY = quality-adjusted life-year.

Budget Impact

CADTH identified the following key limitations with the sponsor's analysis: patient characteristics in the budget impact analysis did not align with the cost-utility analysis; distribution of the DFCI 11-001 trial protocol for the pediatric population was not representative of clinical practice; and the pricing, availability, and accessibility of pegaspargase across Canada is uncertain.

CADTH reanalysis included updating the distribution of the trial protocol for the pediatric population to align with the COG AALL07P4 trial. Under this change, the CADTH reanalysis reported that the reimbursement of calaspargase pegol as a component of MAC for the treatment of patients with ALL would be associated with a budgetary increase of $913,376 in year 1, $1,841,318 in year 2, and $1,856,090 in year 3, with a 3-year total of $4,610,784. This may underestimate the budget impact of reimbursing calaspargase pegol given the uncertainty associated with the price and availability of pegaspargase across Canada.

pERC Information

Members of the committee: Dr. Maureen Trudeau (Chair), Mr. Daryl Bell, Dr. Phillip Blanchette, Dr. Kelvin Chan, Dr. Matthew Cheung, Dr. Michael Crump, Dr. Jennifer Fishman, Mr. Terry Hawrysh, Dr. Yoo-Joung Ko, Dr. Christian Kollmannsberger, Dr. Catherine Moltzan, Ms. Amy Peasgood, Dr. Anca Prica, Dr. Adam Raymakers, Dr. Patricia Tang, Dr. Marianne Taylor, and Dr. W. Dominika Wranik

Meeting date: October 11, 2023

Regrets: None

Conflicts of interest: None

ISSN: 2563-6596

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.