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Reimbursement Recommendation

Blinatumomab (Blincyto)

Indication: For the treatment of patients with Philadelphia chromosome–negative, CD19-positive B-cell precursor acute lymphoblastic leukemia in the consolidation phase of multiphase chemotherapy

Sponsor: Amgen Canada Inc.

Final recommendation: Reimburse with conditions

Summary

What Is the Reimbursement Recommendation for Blincyto?

Canada's Drug Agency (CDA-AMC) recommends that Blincyto be reimbursed by public drug plans for the treatment of patients with Philadelphia chromosome (Ph)–negative, CD19-positive B-cell precursor acute lymphoblastic leukemia (ALL) in the consolidation phase of multiphase chemotherapy if certain conditions are met.

Which Patients Are Eligible for Coverage?

Blincyto should only be covered to treat adult and pediatric patients whose Ph-negative, CD19-positive B-cell ALL is in remission, regardless of whether patients still have detectable traces of cancer (minimal residual disease [MRD]). Remission is a response to treatment in which signs of cancer have disappeared, but it does not always mean the cancer is cured. Remission encompasses complete remission (CR) or CR with incomplete peripheral blood count recovery (CRi), which means the disease is in CR, but blood cell levels have not yet fully returned to normal. Blincyto should be initiated in the front-line consolidation phase of multiphase chemotherapy (treatment phase to improve remission).

What Are the Conditions for Reimbursement?

Blincyto should only be reimbursed if it is prescribed by clinicians with expertise in managing ALL in specialized cancer centres and if the cost of Blincyto is reduced.

Why Did CDA-AMC Make This Recommendation?

- Evidence from a clinical trial in adults demonstrated that patients lived longer and experienced a delay in the return of their cancer when Blincyto was added to chemotherapy compared with chemotherapy alone. Evidence from a clinical trial in pediatric patients suggested that patients experienced a delay in their disease returning when Blincyto was added to chemotherapy compared with chemotherapy alone.
- Blincyto addresses the unmet needs of patients by delaying disease progression, offering a manageable toxicity profile and providing an additional treatment option. The opportunity to administer Blincyto at home has the potential to improve patients' and caregivers' quality of life.
- Based on the CDA-AMC assessment of the health economic evidence, Blincyto may not represent good value to the health care system at the public list price, given uncertainty in subgroup analyses. Therefore, a price reduction is required.

Summary

- Based on public list prices, Blincyto is estimated to cost the public drug plans approximately $66 million for adult patient populations and $36 million for pediatric patient populations over the next 3 years.

Additional Information

What Is Acute Lymphoblastic Leukemia?

ALL is a rare and aggressive blood cancer in which immature and abnormal blood cells grow rapidly in the bone marrow and blood. In B-cell ALL, the white blood cells, called B cells, grow out of control. In patients with Ph-negative disease, cancer cells do not have an abnormal Ph chromosome. In 2019 alone, 440 people were newly diagnosed with ALL in Canada (excluding Quebec); between 2015 and 2017, the 5-year net survival for patients in Canada aged 15 to 99 years was 47%. Although ALL is the least common type of leukemia in adults, it is the most prevalent cancer among children and young adults. The B-cell phenotype is the most common type of ALL.

Unmet Needs in Acute Lymphoblastic Leukemia

There is a significant unmet need for more effective and less toxic therapies that achieve CR, prevent relapses, provide long-term survival, improve quality of life, and minimize the need for frequent hospital visits.

How Much Does Blincyto Cost?

Treatment with Blincyto is expected to cost approximately $83,391 per patient per cycle for adult patients and $46,289 per patient per cycle for pediatric patients.

Recommendation

The pan-Canadian Oncology Drug Review Expert Review Committee (pERC) recommends that blinatumomab be reimbursed for the treatment of patients with Ph-negative, CD19-positive B-cell ALL in the consolidation phase of multiphase chemotherapy if the conditions listed in Table 1 are met.

Rationale for the Recommendation

Evidence from 2 phase III, open-label, randomized, active-controlled trials (E1910 in adult patients and AALL1731 in pediatric patients) showed that blinatumomab, when added to front-line multiphase consolidation chemotherapy (blinatumomab plus chemotherapy), results in added clinical benefit in patients with Ph-negative, CD19-positive B-cell ALL. The E1910 trial demonstrated that, compared with chemotherapy, blinatumomab plus chemotherapy was associated with statistically significant and clinically meaningful improvements in overall survival (OS) after a median follow-up time of 4.5 years in adult patients with MRD-negative disease (hazard ratio [HR] = 0.44; 95% confidence interval [CI], 0.25 to 0.76); medians were not reached in either group). OS rates at 5 years were 82.4% (95% CI, 73.7% to 88.4%) for blinatumomab plus chemotherapy and 62.5% (95% CI, 52.0% to 71.3%) for chemotherapy alone. The results observed in the primary analysis of OS were supported by clinically meaningful improvements in secondary outcomes — relapse-free survival (RFS) in patients with MRD negativity and OS and RFS in patients with MRD positivity — as well as post hoc analyses of OS and RFS in the overall population (combined MRD-negative and MRD-positive populations). The post hoc OS rates at 5 years were 79.1% (95% CI, 71.4% to 85.0%) and 58.3% (95% CI, 48.8% to 66.7%) in the blinatumomab plus chemotherapy group and chemotherapy group, respectively. Results from the AALL1731 trial suggested clinically meaningful improvements in disease-free survival (DFS) after a median follow-up time of 2.5 years in pediatric patients with standard-risk Ph-negative B-cell ALL; DFS rates at 3 years were 96.0% (standard error [SE] = 1.2%) and 87.9% (SE = 2.1%) in the blinatumomab plus chemotherapy group and chemotherapy group, respectively. pERC noted uncertainty whether blinatumomab plus chemotherapy would prolong survival in pediatric patients due to insufficient follow-up time to capture long-term OS benefit. pERC considered the safety profile of blinatumomab plus chemotherapy to be manageable and consistent with the known safety profile of its individual treatment components.

Patients identified a need for treatment options that delay disease progression, improve quality of life, and have manageable side effects. pERC concluded that blinatumomab plus chemotherapy met some of the patients' needs because it delays disease progression, has a manageable toxicity profile, and provides an additional treatment option. Although health-related quality of life (HRQoL) was not evaluated in either of the studies (E1910 or AALL1731), patient input suggested a treatment that delays disease progression with manageable side effects and the opportunity to administer blinatumomab treatment at home have the potential to improve patients' and caregivers' HRQoL.

Using the sponsor-submitted price for blinatumomab and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) for blinatumomab plus standard of care (SOC) in the combined

pediatric and adult population was $37,111 per quality-adjusted life-year (QALY) gained compared with SOC alone. At this ICER, blinatumomab is cost-effective at a willingness-to-pay threshold of $50,000 per QALY gained for patients with Ph-negative, CD19-positive B-cell ALL in the consolidation phase of multiphase chemotherapy. The overall results were influenced largely by the predicted survival benefit in the adult population. Subgroup analyses demonstrated that the ICER significantly differed among adult and pediatric populations, with an ICER in the adult population being $27,682 per QALY gained compared with $508,738 per QALY gained in the pediatric population.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Treatment with blinatumomab should be reimbursed in adult and pediatric patients with newly diagnosed Ph-negative, CD19-positive B-cell ALL in the front-line consolidation phase of multiphase chemotherapy with documented CR or CRi after induction therapy.	Evidence from the E1910 and AALL1731 trials showed that blinatumomab plus chemotherapy compared with chemotherapy alone resulted in clinical benefit in patients with these characteristics.	Adult and pediatric patients who are eligible for conventional chemotherapy should also be eligible for blinatumomab reimbursement regardless of ECOG performance status. Treatment duration with blinatumomab consolidation therapy is up to 4 cycles in adult patients and up to 2 cycles in pediatric patients, both newly diagnosed with Ph-negative, CD19-positive B-cell ALL regardless of MRD status. In the E1910 trial for adult patients, blinatumomab consolidation was administered for 4 cycles. In the AALL1731 trial for pediatric patients, blinatumomab consolidation was administered for 2 cycles.
2. Patients must not have any of the following criteria: 2.1. acute undifferentiated leukemia 2.2. Burkitt leukemia.	There is no evidence from the E1910 and AALL1731 trials to suggest a benefit of blinatumomab plus chemotherapy compared with chemotherapy alone in these patients because patients with these characteristics were not eligible to enrol in these trials.	—
Discontinuation		
3. Treatment with blinatumomab plus chemotherapy should be discontinued upon occurrence of any of the following: 3.1. disease progression 3.2. intolerable toxicity.	These conditions correspond with the criteria used to determine whether treatment with blinatumomab plus chemotherapy was discontinued in the E1910 and AALL1731 trials.	—
Prescribing		
4. Blinatumomab plus chemotherapy should be prescribed by clinicians	This is meant to ensure that blinatumomab plus chemotherapy is prescribed for appropriate	—

Reimbursement condition	Reason	Implementation guidance
with expertise in managing ALL in specialized cancer centres.	patients and that adverse effects are managed in an optimal and timely manner. The clinical experts noted that specialist care at an oncology centre is required due to the pharmacy, nursing, and monitoring requirements for blinatumomab infusions.	
5. Blinatumomab should only be reimbursed when added to front-line multiphase consolidation chemotherapy.	Clinical experts noted that chemotherapy treatment protocols have evolved over time for adult and pediatric patients with Ph-negative B-cell ALL. The clinical experts did not anticipate differential treatment effects of blinatumomab when combined with chemotherapy treatment protocols other than those used in the E1910 or AALL1731 trials.	—
Pricing		
6. A reduction in price.	Using results for the combined adult and pediatric population, blinatumomab plus chemotherapy may be cost-effective at a WTP threshold of $50,000 per QALY gained. However, the overall results were largely driven by the predicted benefit in the adult population. The subgroup analysis considering only the pediatric population resulted in an ICER that exceeded the threshold of $50,000 per QALY gained. A price reduction may reduce the uncertainty regarding the cost-effectiveness of blinatumomab in the pediatric setting.	—
Feasibility of adoption		
7. The organizational feasibility of delivering blinatumomab must be addressed.	Blinatumomab is administered as a continuous IV infusion using specialized ambulatory pumps. This delivery method is expected to place greater demands on health system resources compared with standard of care. Jurisdictions may need to increase the availability of infusion pumps to accommodate higher patient volumes. Although jurisdictions are generally familiar with the preparation, administration, and training requirements for blinatumomab, its adoption at scale may require additional infrastructure planning.	—

ALL = acute lymphoblastic leukemia; CR = complete remission; CRi = complete disease remission with incomplete peripheral blood count recovery; ECOG = Eastern Cooperative Oncology Group; ICER = incremental cost-effectiveness ratio; MRD = minimal residual disease; Ph = Philadelphia chromosome; QALY = quality-adjusted life-year; WTP = willingness to pay.

Discussion Points

- **Significant unmet need:** pERC deliberated on blinatumomab plus chemotherapy considering the criteria for significant unmet need that are described in the Procedures for Reimbursement Reviews. ALL is a rare and aggressive disease with significant mortality and morbidity in adult and pediatric patients. Reflecting on input from clinical experts and patients, pERC acknowledged the importance of ensuring successful front-line therapy to reduce the risk of disease relapse and the need for subsequent therapy, such as allogeneic stem cell transplantation (SCT), which carries significant risk of morbidity and mortality. pERC considered that the evidence from the E1910 trial (in adult patients) and the AALL1731 trial (in pediatric patients) reasonably suggests that blinatumomab plus chemotherapy compared with chemotherapy alone results in clinically meaningful survival benefits in adult and pediatric patients.
- **Efficacy:** The Grading of Recommendations Assessment, Development and Evaluation (GRADE) certainty of evidence assessment resulted in a rating of “high” to “moderate” for the survival outcomes, OS and RFS, in the E1910 trial. The committee discussed that the AALL1731 trial was stopped early based on interim data suggesting improvements in DFS in patients in the blinatumomab plus chemotherapy group. Although pERC agreed with the clinical experts that the delay in DFS observed in pediatric patients receiving blinatumomab plus chemotherapy compared with chemotherapy alone in the AALL1731 trial was clinically meaningful, pERC noted that OS results in the AALL1731 trial were immature and suggested little to no difference between treatment groups. pERC heard from the clinical experts that a longer follow-up would likely be needed to observe notable OS differences between study groups due to the use of salvage therapies in the pediatric patient population; however, these therapies carry a significant risk of morbidity and mortality. pERC discussed that HRQoL was not evaluated in either trial. Reflecting on patient group input as well as on the rarity of the disease and the poor long-term prognosis after disease relapse, pERC concluded that the available evidence meets patient needs based on clinically meaningful delays in disease progression.
- **Generalizability:** pERC discussed that the AALL1731 trial was restricted to patients aged 1 year to 10 years with standard-risk Ph-negative B-cell ALL. Although there was no clinical evidence reviewed for patients younger than 1 year, patients aged 10 to 18 years, or patients with high-risk B-cell ALL, pERC acknowledged the input from the clinical experts that it would be reasonable to generalize the AALL1731 results to these patients because they are similarly managed in clinical practice as those included in the AALL1731 trial. Similarly, although the E1910 trial restricted inclusion to patients aged 30 to 70 years, pERC acknowledged the clinical expert input that results could be generalized to all adults eligible for chemotherapy regardless of age.
- **Adverse events:** pERC discussed the safety profile observed with blinatumomab when added to front-line multiphase consolidation chemotherapy in the E1910 and AALL1731 trials and noted that it was overall consistent with the known safety profile of blinatumomab in adult and pediatric patients with Ph-negative B-cell ALL. In the E1910 trial, overall treatment-emergent adverse events (TEAEs) (of any grade and grade 3 or higher) occurred with similar frequency in patients treated

with blinatumomab plus chemotherapy compared with those receiving chemotherapy alone in the overall population. Neutrophil count and platelet count decrease, anemia, diarrhea, vomiting, and febrile neutropenia were among the most commonly reported TEAEs (of any grade and grade 3 or higher) in patients receiving blinatumomab plus chemotherapy. Although more patients experienced serious adverse events (SAEs) while on blinatumomab plus chemotherapy, treatment discontinuation due to AEs was rare across both study groups. Safety results in the AALL1731 trial appeared largely consistent with those in the E1910 trial; febrile neutropenia and other infections were the most commonly reported TEAEs of grade 3 or higher in pediatric patients receiving blinatumomab plus chemotherapy.

- **Comparator:** pERC noted that multiphase chemotherapy treatment protocols have evolved over time for adult and pediatric patients with Ph-negative B-cell ALL. pERC acknowledged that the clinical experts did not anticipate differential treatment effects of blinatumomab when combined with chemotherapy treatment protocols other than those used in the E1910 or AALL1731 trials. pERC also discussed that CADTH issued a positive recommendation with conditions for blinatumomab in 2020 for patients with Ph-negative B-cell ALL in first or second hematologic CR with MRD greater than or equal to 0.1%. The previous indication for blinatumomab partially overlaps with the indication currently under review; differences include (previous versus current indication): remission status (first and second remission versus first remission), MRD status (MRD ≥ 0.1% versus no MRD restriction), administration schedule (sequential cycles versus alternating with consolidation chemotherapy), and number of cycles of blinatumomab treatment for pediatric patients (maximum of 4 versus 2 cycles of blinatumomab). pERC heard from the clinical experts that they anticipated blinatumomab to have similar efficacy and safety as per previous and current indications; the choice between both blinatumomab indications should be left to the treating clinician and their patient.
- **Economic evidence:** The results of the cost-utility analysis represent the combined results of the adult and pediatric populations for which the expected costs and outcomes for blinatumomab plus chemotherapy and chemotherapy alone differed between subgroups. The overall results were influenced largely by the predicted survival benefit in the adult population. Subgroup analyses demonstrated that the ICER in the adult population was $27,682 per QALY gained compared with $508,738 per QALY gained in the pediatric population. For the pediatric population, because blinatumomab plus chemotherapy is not cost-effective at a willingness-to-pay threshold of $50,000 per QALY gained, a price reduction may reduce the uncertainty regarding the cost-effectiveness of blinatumomab in the pediatric setting.

Background

ALL is a rare and aggressive hematologic malignancy of undifferentiated lymphoid precursors characterized by the proliferation of immature and abnormal lymphoid cells in the bone marrow and peripheral blood. In 2019 alone, 440 people were newly diagnosed with ALL in Canada (excluding Quebec); between 2015 and 2017 the 5-year net survival for patients aged 15 to 99 years in Canada was 47%. Although ALL is the least

common type of leukemia in adults, it is the most prevalent cancer among children and young adults. B-cell phenotype is the most common type of ALL, accounting for approximately 85% of pediatric ALL diagnoses and approximately 75% of adult ALL diagnoses. The leukemia cells in many patients with B-cell ALL have chromosomal abnormalities; one of the most prevalent abnormalities occurs in the Ph chromosome (occurring in 1% to 3% of childhood ALL diagnoses and 11% to 29% of adult ALL diagnoses). Determining the ALL subtype and presence of chromosomal abnormalities is critical for understanding the disease status, risk factors, and treatment planning. In addition, MRD assessments provide information on the prognosis and chance of relapse, with higher MRD levels indicating greater chances of relapse. MRD testing by flow cytometry is widely available in Canada and recommended for patients with ALL. MRD testing is routinely performed; although it is publicly funded in pediatric patients with ALL, funding for MRD testing is not uniform across Canada for adult patients.

Although conventional regimens differ in terms of specific drug selection, dosing, and duration, they all typically include 3 phases during which intensive multiagent chemotherapy protocols are used: induction, consolidation (sometimes called “intensification”), and maintenance. However, not all patients respond to available conventional treatments. Relapse remains a substantial risk, and many patients experience toxicity-related adverse events (AEs). Patients with ALL experience a variety of symptoms, including fatigue, dry mouth, lack of appetite, irritability, and nervousness.

Blinatumomab has been approved by Health Canada for the treatment of patients with Ph-negative, CD19-positive B-cell ALL in the consolidation phase of multiphase chemotherapy. Blinatumomab is a bispecific T-cell engager, available as 38.5 mcg powder for solution for infusion per vial. The Health Canada–recommended dosage is 28 mcg/day for patients weighing 45 kg or more, or 15 mcg/m^2 per day for patients weighing less than 45 kg. Blinatumomab is delivered as continuous IV infusion at a constant flow rate using an infusion pump for 28 days followed by a 14-day treatment-free interval.

Sources of Information Used by the Committee

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

- a review of 2 randomized controlled trials (RCTs), 1 in adult patients and 1 in pediatric patients with Ph-negative B-cell ALL
- patients’ perspectives gathered by 4 patient groups, 1 input was received from Leukemia & Lymphoma Society of Canada (LLSC) and 1 input was a joint submission from LLSC, the Advocacy for Canadian Childhood Oncology Research Network (Ac2orn), Ontario Parents Advocating for Children with Cancer (OPACC), and Childhood Cancer Canada
- input from public drug plans that participate in the reimbursement review process
- input from 2 clinical specialists with expertise diagnosing and treating patients with Ph-negative B-cell ALL, 1 clinical expert specializes in adult ALL and the other focuses on pediatric ALL

- input from 3 clinician groups, Ontario Health − Cancer Care Ontario (OH-CCO) Hematology Cancer Drug Advisory Committee, Pediatric Oncology Group of Ontario (POGO), and Canadian Leukemia Study Group (CLSG)/Groupe Canadien d'Étude Sur La Leucémie (GCEL)
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Perspectives of Patients, Clinicians, and Drug Programs

The information in this section is a summary of input provided by the patient and clinician groups who responded to our call for input and from clinical experts consulted by the purpose of this review.

Patient Input

CDA-AMC received 2 inputs from patient groups for this submission. The first input, provided by LLSC, included survey results from adult patients with ALL and their caregivers. The second input was a joint submission provided by LLSC, Ac2orn, OPACC, and Childhood Cancer Canada and was based on interviews with 3 caregivers of pediatric patients with B-cell ALL who received blinatumomab treatment. The patient group input for pediatric patients was supplemented with information on disease experience and experience with currently available treatments gathered from previous patient group submissions to CDA-AMC for blinatumomab for pediatric patients with Ph-negative B-cell ALL in the relapsed or refractory setting (pCODR 10099 Blinatumomab ALL for pediatrics in 2017 and PX0367 Blinatumomab for ALL for pediatrics in 2024).

LLSC is a national charity organization dedicated to finding a cure for blood cancers and improving the quality of life of people affected by blood cancers and their families by funding research and providing educational resources, services, and support. Ac2orn is a national organization committed to advocating translational research and effective treatments to realize the goal of curing childhood, adolescent, and young adult cancers. OPACC advocates for families and organizations navigating the childhood cancer journey. Childhood Cancer Canada supports children diagnosed with cancer and their families.

Input received for adults with ALL is summarized first followed by patient input from caregivers of pediatric patients with ALL.

LLSC conducted a survey in October and November 2024. The respondents were patients with ALL (69%) and their caregivers (28%). Of 103 respondents who provided their age, 9% were aged 0 to 17 years and were disqualified from the survey. The survey respondents included 49% aged 18 to 39 years, 32% aged 40 to 64 years, 8% aged 65 to 74 years, and 3% older than 75 years. Almost all respondents were from Canada, 1 was from the US, and 1 was international. A negative to very negative impact on personal or home life due to ALL was reported by 82% of respondents. When considering their social life, 75% of respondents reported negative to very negative impact due to ALL. Low energy, fear of infections, frequent hospital visits, depression or anxiety, ALL symptom burden, and inadequate nutrition were reported as factors contributing to the negative impact of ALL.

Eighteen respondents to the LLSC survey had experience with blinatumomab. Among all other types of treatment, chemotherapy was the most commonly reported type of ALL treatment (98% of respondents) followed by SCT (48% of respondents), radiation therapy (45% of respondents), immunotherapy (27% of respondents), targeted therapy (7% of respondents), chimeric antigen receptor (CAR) T-cell therapy (5% of respondents), and other types (16% of respondents; including natural medicine, Chinese medicine, sound baths, meditation, transfusions, steroids, and antiemetics). Fatigue and neutropenia were reported by the respondents as the most severe side effects of current treatments (excluding blinatumomab) followed by thrombocytopenia, infections, nausea, vomiting, diarrhea, anemia, fever, peripheral edema, headaches, infusion reactions, neurologic symptoms, and cytokine release syndrome (CRS). These side effects had substantial impacts on patients' lives, including frequent hospitalizations and lower functionality. According to LLSC, important outcomes for patients include longer remission, manageable side effects, and improved quality of life. Respondents indicated that they also consider financial costs when selecting a new cancer treatment.

According to the LLSC input, 18 respondents stated that they or the person they care(d) for were treated with blinatumomab for ALL. Of the 18 respondents with experience with blinatumomab, 33% and 27% of respondents, respectively, accessed blinatumomab through clinical trials and compassionate use programs the remainder of respondents accessed blinatumomab through private insurance, Régie de l'assurance maladie du Québec (RAMQ) - Quebec socialized health care, government funding, or they did not know. Of 15 respondents, 67%, 20%, and 13% of respondents believed that their ALL completely responded, partially responded, or did not respond to blinatumomab, respectively. Respondents were asked to rate the severity of the side effects of blinatumomab (from 1 = did not experience to 4 = severe). Among 15 respondents, the highest-rated side effects (from 1 = did not experience to 4 = severe), as measured by weighted averages, were neutropenia (2.29), fatigue or weakness (2.27), and fever (2), followed by anemia (1.71), thrombocytopenia (1.71), infections (1.64), headaches (1.57), neurologic symptoms (i.e., confusion, seizures, difficulty speaking; 1.53), CRS (1.5), diarrhea (1.47), peripheral edema (1.47), nausea or vomiting (1.4), and infusion reactions (i.e., chills, rash, difficulty breathing; 1.27). Comparing blinatumomab with other treatments, 40% of 15 respondents felt it was as difficult to tolerate as other treatments, 27% felt it was less or much less difficult, and 7% felt it was more difficult to tolerate. Additionally, 40% of 15 respondents strongly agreed that blinatumomab improved their quality of life compared to other treatments; 20% agreed, 33% felt neutral, and 7% disagreed. Most patients indicated that they were likely to take blinatumomab again or recommend it to other patients.

The joint patient group input for pediatric patients gathered information through interviews with 3 caregivers of pediatric patients with B-cell ALL. According to this patient group submission, the interviews were focused on experiences and quality of life associated with blinatumomab treatment to avoid repetitive questioning and to minimize emotional strain and undue harm. For all other information, this patient group input referred to previous joint submissions to CDA-AMC from LLSC, Ac2orn, OPACC for relapsed or refractory ALL in pediatric patients. First, the following presents the disease experience and experience with currently available treatments gathered from previous patient input submissions. Second, it summarizes patients' and caregivers' experience with blinatumomab treatment and patients' quality of life during blinatumomab

treatment compared with their experience with prior treatments for pediatric ALL based on the joint patient group submission for this current review.

Based on input gathered in previous patient input submissions to CDA-AMC for pediatric patients with relapsed or refractory ALL, children may experience a variety of symptoms, including severe fatigue, pain, high fevers, bleeding, bruising, bone pain, and swollen lymph nodes. However, the impacts of pediatric cancer relapse on the child and their family extend beyond physical symptoms. It was highlighted in the patient group submissions that relapse and immunosuppression severely limit children's ability to engage in normal activities, placing a significant emotional and physical burden on both the child and their family. Families experience intense stress, financial strain, and disrupted daily routines, with caregivers often facing severe impacts on their mental health. It was explained in the patient group submissions that the SOC for treating relapsed or refractory pediatric ALL typically involves a combination of strategies, including drug therapy and radiation. For patients with refractory disease, these aggressive treatments often result in serious side effects, such as immunosuppression, severe pain, infections, anemia, and organ damage, which can significantly impact the child's quality of life. There is a significant unmet need for more effective, less toxic therapies that improve quality of life by reducing treatment burden and minimizing the need for frequent hospital visits. Outpatient treatment options that reduce hospital stays were also cited as being crucial for maintaining normalcy and reducing stress for both patients and their families. In terms of improved outcomes, it was noted in the patient group submissions that patients and their families are looking for options that are not only effective but also gentle on their children. They seek innovative therapies that can provide significant benefits without causing undue harm or severe side effects. Additionally, having these treatments covered by drug plans is crucial because it alleviates the financial burden on families.

In the 3 caregiver interviews conducted in the joint patient group submission for this review, 2 of the caregivers had children who were 2 years old at diagnosis and 1 had a child who was 10 years old at diagnosis. Two caregivers were residents of Ontario, and 1 resided in British Columbia. The input focused on patients' and caregivers' experiences with administering blinatumomab treatment at home, as well as on comparing their quality of life during blinatumomab treatment to their experiences with prior treatments for pediatric ALL. According to the joint submission, the current conventional therapy for pediatric patients with B-cell ALL living in Canada is chemotherapy infusions, which is often accompanied by serious side effects, negative impact on patients' physical health, and long hospital stays. Based on the joint input, all 3 caregivers mentioned that they and their children had overall positive experiences with blinatumomab, especially compared with chemotherapy infusion. Due to outpatient treatment and the "gentler" effects of blinatumomab, the patients were able to live with family, play with peers, and stay out of the hospital. According to the patient group input, cognitive testing was done routinely at every blinatumomab bag change to check for neurologic AEs; none of the caregivers reported neurologic AEs as a side effect in their children. The caregivers reported an extra burden from having to obtain a new blinatumomab medication bag every 4 days and having to visit the medical centre for any glitches in the blinatumomab delivery system. Caregivers noted that knowledge of blinatumomab's delivery method was limited among health care professionals due to it being a relatively new treatment method. Some caregivers emphasized the need for greater variety for

the backpack delivery system for blinatumomab that would be able to accommodate pediatric patients of all ages.

According to the joint submission, all 3 caregivers related that blinatumomab made a big difference to the quality of life for their children, themselves, and the rest of their families compared with traditional chemotherapy infusion. Financial stress was experienced by caregivers due to the high cost and lack of public funding for blinatumomab. Finally, the joint submission made the following suggestions for improved outcomes with new therapies:

- Provide caregivers with tips and tools on what to expect with the blinatumomab delivery system and some at-home solutions to help alleviate practical challenges such as driving to cancer centres at unexpected times.
- Train nurses at local hospitals on administering blinatumomab (to mitigate the requirement of driving to cancer centres).
- Improve blinatumomab knowledge and skills of the nurses at the cancer centres.
- Provide more choices in the delivery system backpacks that are based on the body size and strength of the patient.

Clinician Input

Input From Clinical Experts Consulted for This Review

Two clinical specialists with expertise in the diagnosis and management of Ph-negative B-cell ALL provided input for this review. One of the clinical experts had specific expertise in the diagnosis and management of adult patients with Ph-negative B-cell ALL whereas the other had expertise with pediatric patients with Ph-negative B-cell ALL.

Both clinical experts felt the overarching goal of Ph-negative B-cell ALL treatment is the to achieve CR, prevent relapses, and cure the disease (thus improving long-term survival), all while minimizing acute and late toxicities. The experts highlighted that not all patients respond to available conventional treatments, relapse remains a substantial risk, and many patients experience toxicity-related AEs. The clinical experts consulted for this review noted that unplanned inpatient admissions due to complications associated with the current conventional treatments are common. Further, because ALL is the most common childhood cancer, the clinical expert with experience treating pediatric patients with ALL highlighted that decreasing relapse rates in ALL would have a significant impact on childhood cancer mortality rates and obviate the need for additional expensive and/or toxic therapies.

Both clinical experts consulted for this review felt that blinatumomab would add an alternative first-line treatment option for patients with Ph-negative B-cell ALL. The experts recommended using 1 to 4 cycles of blinatumomab in sequence with conventional consolidation chemotherapy. Compared with current treatment options, the clinical experts noted that blinatumomab's unique mechanism of action blocking CD19 antigens expressed on the leukemic blasts has the potential to improve overall response rate, RFS, and OS while decreasing AEs associated with the frequent use of intensive chemotherapy and, in turn, potentially improving quality of life for patients with Ph-negative B-cell ALL. If blinatumomab reduces the use

of allogeneic SCT by preventing relapse, the clinical experts noted that the risk of treatment-related mortality may also decrease.

The clinical experts consulted for this review noted any adult or pediatric patient with Ph-negative B-cell ALL who achieves CR following induction therapy, regardless of risk (MRD and standard-risk, high-risk, or very high–risk status) and age, would be best suited for first-line consolidation treatment with blinatumomab.

The clinical expert with experience treating pediatric patients noted that the 1 exception may be to exclude pediatric patients from receiving blinatumomab if their expected event-free survival on a particular conventional chemotherapy backbone is expected to be greater than 95% (i.e., those with standard risk and a favourable risk of relapse). However, the experts flagged that the molecular characterization of leukemia is rapidly evolving, and the identification of a new high-risk somatic change may alter how patients are currently classified.

The expert felt that adult patients with Ph-negative B-cell ALL who have a poor performance status (i.e., Eastern Cooperative Oncology Group [ECOG] performance status > 2) should not be eligible for blinatumomab, whereas no performance status restriction should be made in children because blinatumomab has been shown to be well tolerated and potentially lifesaving. Clinical experts felt there was insufficient data to recommend blinatumomab treatment in patients with acute undifferentiated leukemia and those with Burkitt leukemia.

The clinical experts consulted for this review noted that treatment response is based on bone marrow evaluation (including morphological evaluation and MRD assessment) at the end of induction and consolidation treatment. RFS, DFS, OS, and other survival parameters, such as relapse incidence, are long-term parameters used to assess treatment response in both clinical trials and clinical practice. In both clinical trials and clinical practice, AEs are used to assess treatment benefit. The clinical expert with experience treating adults with ALL noted that after the completion of maintenance treatment, relapse is assessed every 3 months during the first year, every 6 months during the second year, and then annually between years 3 and 5. The clinical expert with experience treating pediatric patients with ALL noted that follow-up practices vary by centre after the completion of maintenance treatment; however, in their clinical practice, relapse is assessed monthly for the first 3 months, then every third month during the first year, every 4 months in the second year, every 6 months in the third year, and then annually for the rest of the patient's life.

As in the clinical trial and per blinatumomab's label, the clinical experts consulted for this review noted that blinatumomab should be discontinued in the event of grade 4 CRS, grade 4 neurotoxicity or psychiatric events, and grade 4 thrombosis. Other grade 4 toxicities that are deemed clinically significant may require discontinuation of blinatumomab. Toxicities that require dose interruption of blinatumomab that do not return to grade 1 or lower by 14 days (or by 7 days in the case of neurotoxicity) necessitate discontinuation of blinatumomab. Recurrent toxicities leading to dose interruption of blinatumomab also require permanent discontinuation of blinatumomab.

The clinical expert with experience treating adult patients with ALL noted that patients who develop any debilitating conditions (e.g., ECOG performance status > 2) should discontinue blinatumomab treatment.

Although the clinical experts agreed with the discontinuation criteria listed previously, the benefits of treatment, availability of alternative treatments, risks of discontinuation, and patients' willingness to continue treatment must also be taken into account before making a final discontinuation decision. In adult patients, the expert felt that blinatumomab should be discontinued in the event of disease progression and relapse and upon the patient's request.

Both clinical experts indicated that treatment with blinatumomab should initiate on an inpatient basis (3 days for the first infusion and 2 days for subsequent infusions) and, if it is well tolerated, subsequent infusions can be performed in an outpatient clinic. Because of the pharmacy, nursing, and monitoring requirements for blinatumomab infusions, specialist care at an oncology centre is required. Both clinical experts consulted for this review felt that any conventional chemotherapy used for ALL treatment can be combined with blinatumomab. They also felt that clinicians should have the ability to adjust the dosage, number of cycles, and cycle length based on toxicity and individual patient's needs.

The clinical expert with experience treating adult patients noted that at least 2 cycles of blinatumomab should be given before SCT to deepen the patient's remission. SCT would likely be required in adult patients in their second CR (regardless of MRD status) and in adult patients in first CR with continuous MRD positivity and would be considered in adult patients in first CR with MRD-negative status after initially presenting with the highest risk of disease relapse.

Clinician Group Input

Three clinician groups each submitted inputs to CDA-AMC: OH-CCO Hematology Cancer Drug Advisory Committee (with input from 6 clinicians); POGO (input from 11 clinicians); and CLSG-GCEL (input from 7 clinicians). One group provided input relevant to pediatric patients (POGO) and another group provided for adults (CLSG-GCEL); the third group did not specify an age group of patients represented.

The clinician groups were generally in agreement with the feedback received from the clinical experts consulted for this review. In terms of the goals of therapy, the clinical experts and clinician groups indicated the main goals are cure of the disease while minimizing toxicity. Other goals include achieving CR, preventing relapse, and avoiding need for second-line therapies, such as allogenic SCT or CAR T-cell therapy. For pediatric patients, the POGO group stated that relapse therapies carry significant toxicity and can leave young patients with a wide variety of potentially lifelong late effects. For adults, the clinician groups noted the substantial risk of relapse, even in patients with MRD-negative status, thus additional treatments are needed to improve survival, CR, and relapse rate, and minimize or reduce toxicity of treatments (during consolidation and/or later therapies).

All clinician groups agreed that the patient population suitable to receive blinatumomab during consolidation includes those newly diagnosed with Ph-negative, CD19-positive B-cell ALL, regardless of MRD status. Both the pediatric clinical expert consulted for this review and the POGO group indicated that patients who meet the standard risk and average or high risk of relapse stratification criteria have less favourable outcomes with chemotherapy alone and are expected to benefit from the addition of blinatumomab during consolidation therapy. Those who meet the standard risk and favourable risk of relapse stratification criteria have excellent response rates (event-free survival > 95%) with chemotherapy alone and may not require blinatumomab

therapy. The POGO group noted an unmet need for augmentation therapies that have a tolerable adverse effect profile and may allow for cytotoxic "breaks" in therapy to facilitate recovery from cytotoxic-associated complications, such as fungal infections. According to input from POGO, patients with Ph-positive B-cell ALL may also benefit from blinatumomab therapy. The clinician groups agreed that standard response assessment for ALL would be relevant for monitoring the effects of blinatumomab, including MRD status, duration of response, relapse, and OS. The adult clinician groups noted the MRD threshold of 0.1% ($\geq 10^{-3}$) is obsolete, and the current standard is greater than or equal to 0.01% ($\geq 10^{-4}$).

The experts consulted and the clinician groups agreed that blinatumomab would be discontinued if the patient experienced disease progression or significant toxicity, and that specialist care in a treatment centre for ALL is warranted. The POGO group expressed that reimbursement strategies should account for all forms of drug wastage, which may occur when pediatric doses are prepared.

Drug Program Input

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

- considerations for initiation of therapy
- considerations for discontinuation of therapy
- considerations for prescribing of therapy
- generalizability of trial populations to the broader populations in the jurisdictions
- potential need for a provisional funding algorithm
- care provision issues
- system and economic issues.

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

Table 2: Responses to Questions From the Drug Programs

Implementation issues	Response
Relevant comparators	
E1910 (adult trial): Standard ALL chemotherapy regimen (chemotherapy alone) versus ALL chemotherapy with blinatumomab at (consolidation phase) with chemotherapy (4 doses of blinatumomab added to consolidation chemotherapy). COG AALL1731 (pediatric trial): ALL chemotherapy (chemotherapy alone) versus chemotherapy plus blinatumomab in consolidation phase ALL regimen (2 blocks of blinatumomab with consolidation chemotherapy).	This is a comment from the drug programs to inform pERC deliberations.

Implementation issues	Response
Considerations for initiation of therapy	
Ph negativity must be established by conventional cytogenetics (FISH and/or PCR). • For adults, what is the definition of "MRD negative"? What is the minimum threshold value to determine MRD status?	The clinical expert with experience treating adult patients with ALL noted that multiparameter flow cytometry is used to test MRD and has a sensitivity of up to 10^{-4}. The clinical expert stated that not all centres in Canada can achieve a sensitivity of 10^{-4}; however, at a minimum, most in Canada have a sensitivity of 10^{-3} and, as such, MRD negativity should be defined < 0.1%. pERC acknowledged the feedback from the clinical experts.
Adult E1910 trial: Patients aged 30 to 70 years. Pediatric AALL1731 trial: Patients aged 1 year to 10 years. • Should patients > 70 years of age be eligible for treatment provided they do not have contraindications or comorbidities and have completed induction chemotherapy? • Can pediatric patients < 1 years be eligible for treatment? Under what circumstances? • What risk categories are eligible for this treatment in adult and pediatric patients?	pERC agreed with the clinical experts that all adult and pediatric patients who are eligible for conventional chemotherapy should also be eligible for blinatumomab reimbursement regardless of age. pERC agreed with the clinical experts that it would be reasonable to generalize the results from the AALL1731 trial to patients younger than 1 year and those aged 10 to 18 years, which is a patient population included in the Health Canada indication. The blinatumomab product monograph states the following: "Pediatrics (< 18 years of age): The safety and efficacy of BLINCYTO have been established in pediatric patients as young as one month with Ph-negative relapsed or refractory B-cell ALL (p. 4)." The clinical expert with experience treating adult patients with ALL felt that there was sufficient evidence across risk categories to demonstrate that blinatumomab consolidation treatment provides benefit and thus should be reimbursed without restriction to a specific risk. pERC agreed not to limit reimbursement by risk categories. The clinical expert with experience treating children with ALL noted that, except for patients who present with very severe toxicities from leukemia such as sepsis and multiorgan failure, all patients are eligible for conventional chemotherapy. A similar criterion should be used for determining blinatumomab eligibility in pediatric patients. The expert noted that the 1 exception may be to exclude from receiving blinatumomab those pediatric patients with expected event-free survival on a conventional chemotherapy backbone to be greater than 95% (i.e., those with standard-risk B-cell ALL with a favourable risk for relapse). However, the clinical experts cautioned against any restrictions by relapse risk, flagging that the molecular characterization of leukemia is rapidly evolving and the identification of a new high-risk somatic change may alter how patients are currently classified. pERC agreed with the clinical experts with experience treating children not to limit reimbursement by risk categories.
Considerations for discontinuation of therapy	
Discontinuation of blinatumomab at consolidation was due to disease progression or intolerable toxicity.	This is a comment from the drug programs to inform pERC deliberations.
Treatment is for 4 cycles in consolidation for adults. Treatment is for 2 cycles of consolidation in pediatrics.	This is a comment from the drug programs to inform pERC deliberations.

Implementation issues	Response
Considerations for prescribing of therapy	
Blinatumomab is administered via continuous infusion for 28 days via specialized pumps. Programs may need to increase the number of pumps with the increase in patients (newly diagnosed versus relapsed or refractory disease). Jurisdictions are familiar with blinatumomab preparation and administration and training.	This is a comment from the drug programs to inform pERC deliberations.
Generalizability	
Patients with mature B-cell ALL (Burkitt leukemia) were excluded from the E1910 trial. Patients were excluded with acute undifferentiated leukemia in AALL1731. • Would patients with Burkitt leukemia or acute undifferentiated leukemia be eligible for this treatment? • Blinatumomab was given to patients with an ECOG performance status of 0 to 2; would patients with an ECOG status > 2 be eligible to receive blinatumomab at consolidation?	pERC agreed with the clinical experts that there were insufficient data to recommended blinatumomab treatment in patients with acute undifferentiated leukemia and those with Burkitt leukemia. pERC agreed with the clinical expert that adult patients with an ECOG performance status of ≤ 2 are eligible for conventional chemotherapy and a similar criterion should be used for determining blinatumomab eligibility in adults. The clinical expert with experience treating adults with ALL felt that adults with Ph-negative B-cell ALL who have a poor performance status (i.e., ECOG > 2) should not be eligible for treatment with blinatumomab. In the pediatric trial (AALL1731), enrolment was not restricted by performance status and the clinical expert with experience treating children with ALL felt that no performance status restriction should be made in children because blinatumomab has been shown to be well tolerated and potentially lifesaving. pERC agreed not to limit reimbursement criteria by ECOG performance status for children.
Funding algorithm	
Request an initiation of a rapid provisional funding algorithm. Note that if the final reimbursement recommendation for this drug under review is “do not reimburse,” the project will be suspended indefinitely.	This is a comment from the drug programs to inform pERC deliberations.
Drug may change place in therapy of drugs reimbursed in subsequent lines.	This is a comment from the drug programs to inform pERC deliberations.
Complex therapeutic space with multiple lines of therapy, subpopulations, or competing products.	This is a comment from the drug programs to inform pERC deliberations.
Care provision issues	
A single cycle of treatment is 28 days (4 weeks) of continuous infusion followed by a 14-day (2-week) treatment-free interval. Patients may receive up to 4 cycles of blinatumomab consolidation treatment (adult patients) or 2 blocks of blinatumomab (pediatric patients). Blinatumomab infusion bags should be admixed to infuse over 24 hours, 48 hours, 72 hours, 96 hours, or 7 days. Patients weighing ≥ 45 kg receive a fixed dose and, for patients weighing < 45 kg, the dose is calculated using the patient’s BSA. Depending on drug preparation, more than a single vial may be required for a dose and there may be drug wastage.	This is a comment from the drug programs to inform pERC deliberations.

Implementation issues	Response
Patients will start treatment in hospital and then take the pump home. Patients will return to the facility for bag changes (duration varies based on jurisdiction procedures).	
Blinatumomab is associated with adverse effects and will require monitoring by oncologist, nursing, and so on.	This is a comment from the drug programs to inform pERC deliberations.
System and economic issues	
Provision of blinatumomab for patients who are newly diagnosed with Ph-negative ALL may translate into substantial budget impact.	This is a comment from the drug programs to inform pERC deliberations.
This therapy will be administered in centres that provide treatment for adult and pediatric patients with ALL and may not be available in all provinces or territories. Hospitalization is required for the first 3 days of the first cycle and the first 2 days of the second cycle. All subsequent cycles and reinitiation require supervision for the first 4 hours. Centres are familiar with the administration and preparation of blinatumomab.	This is a comment from the drug programs to inform pERC deliberations.
If funded, the upfront cost will have significant budget impacts for the first couple of years as jurisdictions treat newly diagnosed patients, as well as provide blinatumomab for those who have relapsed or refractory ALL (previously funded indications).	This is a comment from the drug programs to inform pERC deliberations.

ALL = acute lymphoblastic leukemia; BSA = body surface area; COG = Children's Oncology Group; ECOG = Eastern Cooperative Oncology Group; FISH = fluorescence in situ hybridization; MRD = minimal residual disease; PCR = polymerase chain reaction; pERC = pan-Canadian Oncology Drug Review Expert Review Committee; Ph = Philadelphia chromosome.

Clinical Evidence

Systematic Review

Description of Studies

One ongoing, phase III, open-label, multicentre, international study (the E1910 trial) met the inclusion criteria for the systematic review conducted by the sponsor. A second phase III, open-label, multicentre, international study (the AALL1731 trial) was included to inform the reimbursement request among pediatric patients.

E1910 Trial

The E1910 trial aimed to evaluate the efficacy and safety of blinatumomab used in the consolidation phase of multiphase chemotherapy for the treatment of adult patients with Ph-negative B-cell ALL and MRD negativity. Secondary outcomes included assessing the efficacy and safety of blinatumomab in patients who were MRD-positive while post hoc analyses were conducted among an MRD-agnostic cohort. Following confirmation of eligibility, all patients completed induction and intensification treatment. CR was defined as a neutrophil count of 1.0 × 10^9/L or greater, platelet count of 100 × 10^9/L or greater, no leukemic blasts present

in the peripheral blood, adequate bone marrow cellularity with trilineage hematopoiesis, 5% or less blasts in the bone marrow, and no extramedullary leukemia (e.g., CNS or soft tissue involvement). CRi had the same definition as CR with the exception of incomplete platelet recovery (i.e., platelets > 75 × 10^9/L and < 100 × 10^9/L) or incomplete neutrophil count recovery (i.e., > 0.75 × 10^9/L and < 1 × 10^9/L]). Patients who achieved CR and CRi were randomized 1:1 using stratified randomization (based on MRD-positive versus MRD-negative status, aged 30 to 54 years versus 55 years or older, CD20-positive versus CD20-negative status, rituximab use versus no use, and intention to receive allogeneic SCT versus not) to receive consolidation treatment with blinatumomab plus conventional chemotherapy (blinatumomab plus chemotherapy) or conventional chemotherapy alone (chemotherapy). Following a protocol amendment related to the FDA-accelerated approval of blinatumomab therapy for patients with MRD-positive disease, these patients were assigned (rather than randomized) to blinatumomab plus chemotherapy. Overall, 286 eligible patients were randomized or assigned to either the blinatumomab plus chemotherapy arm (n = 152) or the chemotherapy arm (n = 134) and included in the step 3 analysis set. The outcomes relevant to this review include OS, RFS, and harms data collected at the primary analysis data cut-off (DCO) date of June 23, 2023.

In the E1910 trial, slightly more patients were female (51.4%) than male (48.6%), the mean age at enrolment was 49.9 years (SD = 11.5 years), and patients were primarily white (79.4%) followed by Black or African American (5.9%), Asian (2.1%), American Indian or Alaska Native (1.0%), Native Hawaiian or other Pacific Islander (0.3%), and either not reported or unknown (4.5% and 6.6%, respectively) race. Most patients had an ECOG performance status of 1 (58.7%), and 37.1% of randomized or assigned patients had an ECOG performance status of 0. Overall, 224 (78.3%) of the randomized or assigned patients had a MRD-negative status and were included in the full analysis set (FAS) (112 [73.7%] in the blinatumomab plus chemotherapy arm and 112 [83.6%] in the chemotherapy arm); 62 (21.7%) had a MRD-positive status and were included in the step 3 MRD-positive analysis set (40 [26.3%] in the blinatumomab plus chemotherapy arm and 22 [16.4%] in the chemotherapy arm).

AALL1731 Trial

The AALL1731 trial aimed to evaluate the efficacy and safety of blinatumomab for the treatment of pediatric patients with standard-risk B-cell ALL. The primary end point was DFS, and the primary objective was to determine whether the addition of blinatumomab (administered as nonsequential cycles) to conventional chemotherapy would improve DFS in all randomized patients with standard-risk B-cell ALL (patients either had an average or high risk of relapse on the basis of clinical features). A post hoc objective was to determine if the addition of blinatumomab to conventional chemotherapy would improve OS in all randomized patients. All eligible patients received induction treatment before undergoing assessments for relapse risk and receiving 1 cycle of consolidation treatment. Only those with standard-risk B-cell ALL and an average risk and high risk of relapse were randomized 1:1 using stratified randomization (based on standard-risk B-cell ALL and an average risk of relapse versus standard-risk B-cell ALL and a high risk of relapse as well as diagnosis of Down syndrome versus no diagnosis of Down syndrome among those with standard-risk B-cell ALL and an average risk of relapse) to blinatumomab plus conventional chemotherapy or conventional chemotherapy alone. Overall, 1,440 eligible patients were randomized to either the blinatumomab plus

chemotherapy arm (n = 718) or the chemotherapy arm (n = 722). The outcomes relevant to this review include OS, DFS, and harms data collected at the interim analysis with DCO on June 30, 2024.

At the planned interim analysis with DCO on June 30, 2024, the Data Safety Monitoring Committee recommended that the blinatumomab randomization be permanently closed based on the 3-year DFS estimates of 96.0% (SE = 1.2%) for the blinatumomab plus chemotherapy arm versus 87.6% (SE = 2.1%) for the chemotherapy alone arm. The associated HR was 0.39 (95% CI, 0.24 to 0.64), which exceeded the prespecified interim efficacy stopping criteria.

In the AALL1731 trial, the median age at randomization was 4.3 years (interquartile range [IQR], 2.8 to 6.4 years). Slightly fewer patients were female (57.4%; 682 of 1,440) than male (52.6%; 758 of 1,440) and patients were primarily non-Hispanic white (50.4%) followed by Hispanic (25.8%), non-Hispanic Black (5.6%), non-Hispanic Asian (4.3%), or other or unknown (13.9%). Overall, 835 (58.0%) of randomized patients had standard-risk B-cell ALL and an average risk of relapse (417 in the blinatumomab plus chemotherapy arm and 417 in the chemotherapy arm) and 605 (42.0%) had standard-risk B-cell ALL and a high risk of relapse (304 in the blinatumomab plus chemotherapy arm and 301 in the chemotherapy arm).

Efficacy Results

Overall Survival

E1910 Trial

In the E1910 trial, the median follow-up duration for OS was 4.5 years in both arms of the step 3 analysis set (i.e., the overall cohort randomized or assigned to 1 of the treatment arms). Death occurred in 30 of 152 patients (19.7%) in the blinatumomab plus chemotherapy arm and 53 of 134 patients (39.6%) in the chemotherapy arm. The Kaplan-Meier (KM) estimate for median OS was not evaluable (NE) in both arms, with a stratified HR of 0.47 (95% CI, 0.30 to 0.74). The between-group difference in the probability of survival for the blinatumomab plus chemotherapy arm versus the chemotherapy arm at 3 and 5 years was 16.9% (95% CI, 5.5% to 28.3%) and 20.8% (95% CI, 8.5% to 33.0%), respectively.

In the FAS (i.e., the MRD-negative cohort) of the E1910 trial, the median follow-up duration for OS was 4.5 years in both arms. Death occurred in 19 of 112 patients (17.0%) in the blinatumomab plus chemotherapy arm and 40 of 112 patients (35.7%) in the chemotherapy arm. The KM estimate for median OS was NE in both arms, with a stratified HR of 0.44 (95% CI, 0.25 to 0.76). The between-group difference in the probability of survival for the blinatumomab plus chemotherapy arm versus the chemotherapy arm at 3 and 5 years was 15.6% (95% CI, 3.0% to 28.2%) and 19.9% (95% CI, 6.3% to 33.5%), respectively.

In the step 3 MRD-positive analysis set (i.e., the MRD-positive cohort) of the E1910 trial, the median duration of OS follow-up was 4.6 years in the blinatumomab plus chemotherapy arm and 5.0 years in the chemotherapy arm. Death occurred in 11 of 40 patients (27.5%) in the blinatumomab plus chemotherapy arm and 13 of 22 patients (59.1%) in the chemotherapy arm. The KM estimate for median OS was NE in the blinatumomab plus chemotherapy arm and was 1.9 months (95% CI, 0.6 months to NE) in the chemotherapy arm; the stratified HR was 0.40 (95% CI, 0.14 to 1.12). The between-group difference in the probability of

survival for the blinatumomab plus chemotherapy arm versus the chemotherapy arm at 3 and 5 years was 31.1% (95% CI, 4.1% to 58.0%) and 32.3% (95% CI, 5.4% to 59.3%), respectively.

AALL1731 Trial

In the AALL1731 trial, the median duration of follow-up was 2.5 years (IQR, 1.6 to 3.2 years). The probability of survival from randomization to 3 years was 98.4% (SE = 0.8%) in the blinatumomab plus chemotherapy arm and 97.1% (SE = 1.1%) in the chemotherapy arm. Between-group differences were not reported (NR). Subgroup analyses among the cohort with an average risk of relapse (probability of survival from randomization to 3 years was 100.0% [SE = not applicable] in the blinatumomab plus chemotherapy arm and 98.4% [SE = 1.0%] in the chemotherapy arm) and high risk of relapse (probability of survival from randomization to 3 years was 96.1% [SE = 2.0%] and 95.3% [SE = 2.2%], respectively) showed similar results.

Relapse-Free Survival

E1910 Trial

In the E1910 trial the median duration of RFS follow-up was 4.5 years in both arms of the step 3 analysis set. A relapse event occurred in 36 of 152 patients (23.7%) in the blinatumomab plus chemotherapy arm and 56 of 134 patients (41.8%) in the chemotherapy arm. The KM estimate for median RFS was NE in both arms, with a stratified HR of 0.53 (95% CI, 0.35 to 0.81). The between-group difference in the probability of RFS for the blinatumomab plus chemotherapy arm versus the chemotherapy arm at 1, 3, and 5 years was 12.2% (95% CI, 1.8% to 22.7%), 17.3% (95% CI, 5.6% to 28.9%), and 18.4% (6.3% to 30.6%), respectively.

In the FAS in the E1910 trial, the median duration of RFS follow-up was 4.5 years in both arms. A relapse event occurred in 25 of 112 patients (22.3%) in the blinatumomab plus chemotherapy arm and 43 of 112 patients (38.4%) in the chemotherapy arm. The KM estimate for median OS was NE in both arms, with a stratified HR of 0.53 (95% CI, 0.32 to 0.88). The between-group difference in the probability of RFS for the blinatumomab plus chemotherapy arm versus the chemotherapy arm at 1, 3, and 5 years was 8.2% (95% CI, −3.0% to 19.4%), 15.4% (95% CI, 2.3% to 28.4%), and 16.5% (95% CI, 2.6% to 30.3%), respectively.

In the step 3 MRD-positive analysis set in the E1910 trial, the median duration of RFS follow-up was 4.6 years in the blinatumomab plus chemotherapy arm and 5.0 years in the chemotherapy arm. A relapse event occurred in 11 of 40 patients (27.5%) in the blinatumomab plus chemotherapy arm and 13 of 22 patients (59.1%) in the chemotherapy arm. The KM estimate for median OS was NE in the blinatumomab plus chemotherapy arm and was 0.6 months (95% CI, 0.2 months to NE) in the chemotherapy arm; the stratified HR was 0.37 (95% CI, 0.13 to 1.03). The between-group difference in the probability of RFS for the blinatumomab plus chemotherapy arm versus the chemotherapy arm at 1, 3, and 5 years was 38.0% (95% CI, 11.6% to 64.5%), 32.4% (95% CI, 6.1% to 58.7%), and 32.4% (95% CI, 6.1% to 58.7%), respectively.

AALL1731 Trial

RFS was not assessed in the AALL1731 trial.

Disease-Free Survival

E1910 Trial

DFS was not assessed in the E1910 trial.

AALL1731 Trial

In the AALL1731 trial, the median duration of follow-up was 2.5 years (IQR, 1.6 to 3.2 years). The probability of remaining disease-free from randomization to 3 years was 96.0% (SE = 1.2%) in the blinatumomab plus chemotherapy arm and 87.9% (SE = 2.1%) in the chemotherapy arm; the associated HR was 0.39 (95% CI, 0.24 to 0.64). The between-group differences in the probability of DFS at 3 years and the KM estimate for median DFS were NR. Subgroup analyses among the cohorts with an average risk and high risk of relapse showed similar results. For the cohort with an average risk of relapse, the probability of DFS from randomization to 3 years was 97.5% (SE = 1.3%) in the blinatumomab plus chemotherapy arm and 90.2% (SE = 2.3%) in the chemotherapy arm and the associated HR was 0.33 (95% CI, 0.15 to 0.69). For the cohort with a high risk of relapse, the probability of survival from randomization to 3 years was 94.1% (SE = 2.5%) in the blinatumomab plus chemotherapy arm and 84.8% (SE = 3.8%) in the chemotherapy arm and the associated HR was 0.45 (95% CI, 0.24 to 0.85).

Harms Results

Safety outcomes for the E1910 trial were thoroughly reported in the data provided to the CDA-AMC review team and are summarized subsequently. For the AALL1731 trial, only the occurrence of grade 3 or greater TEAEs were available for patients who underwent randomization, started postconsolidation protocol therapy, and had data submitted.

In the E1910 trial, harms data are summarized among the step 3 safety analysis set, which includes all patients in the step 3 analysis set who had at least 1 dose of protocol-specified therapy.

Treatment-Emergent Adverse Events

E1910 Trial

By the DCO of June 23, 2023, a similar percentage of patients in both treatment arms of the step 3 safety analysis set in the E1910 trial experienced a TEAE (145 of 147 [98.6%] in the blinatumomab plus chemotherapy arm and 125 of 128 [97.7%] in the chemotherapy arm). The 3 most common TEAEs in the blinatumomab plus chemotherapy arm were investigations (e.g., blood cell counts; 91.8%), blood and lymphatic system disorders (e.g., anemia; 62.6%), and nervous system disorders (e.g., headache; 57.8%). In the chemotherapy arm, the 3 most common TEAEs were investigations (96.9%), blood and lymphatic system disorders (70.3%), and gastrointestinal disorders (e.g., diarrhea; 44.5%).

AALL1731 Trial

TEAEs of any grade in the AALL1731 trial were not provided in the materials reviewed by the CDA-AMC review team.

Grade 3 or Higher TEAE

E1910 Trial

A similar percentage of patients in both treatment arms of the step 3 safety analysis set in the E1910 trial experienced a grade 3 or higher TEAE (141 of 147 [95.9%] in the blinatumomab plus chemotherapy arm and 125 of 128 [97.7%] in the chemotherapy arm). In the blinatumomab plus chemotherapy arm, the 3 most common grade 3 or higher TEAEs were the same as the 3 most common TEAEs of any grade (i.e., investigations [89.8%], blood and lymphatic system disorders [39.5%], and nervous system disorders [22.4%]). In the chemotherapy arm, the 3 most common grade 3 or higher TEAEs were investigations (96.1%), blood and lymphatic system disorders (57.0%), and infection and infestation (e.g., sepsis; 24.2%).

AALL1731 Trial

Generally, it was reported that the percentage of grade 3 or higher TEAEs was well balanced across treatment arms. Notable differences included a higher percentage of patients experienced febrile neutropenia in the blinatumomab plus chemotherapy arms of both the standard-risk B-cell ALL and an average risk of relapse cohort (47.0%; 165 of 351) and the standard-risk B-cell ALL and a high risk of relapse cohort (57.1%; 156 of 273) than in the chemotherapy arms (39.6% [149 of 376] and 50.5% [140 of 277], respectively). Additionally, in the standard-risk B-cell ALL and an average risk of relapse cohort, a higher percentage of patients in the blinatumomab plus chemotherapy arm experienced sepsis or catheter-related infection (14.8%) and other infections (32.8%) than in the chemotherapy arm (5.1% and 26.3%, respectively). In both the standard-risk B-cell ALL and an average risk and high risk of relapse cohorts, the 3 most common grade 3 or higher TEAEs in the blinatumomab plus chemotherapy arms were febrile neutropenia (47.0% and 57.1%, respectively), other infection (32.8% and 35.2%, respectively), and sepsis or catheter-related infection (14.8% and 20.9%, respectively). In both the standard-risk B-cell ALL and an average risk and high risk of relapse cohorts, the 3 most common grade 3 or higher TEAEs in the chemotherapy arms were febrile neutropenia (39.6% and 50.5%, respectively), other infections (26.3% and 37.9%, respectively), and mucositis (15.4% and 17.7%, respectively).

In both the standard-risk B-cell ALL and an average risk and high risk of relapse subgroups, 1 patient in the blinatumomab plus chemotherapy arm and no patients in the chemotherapy arm experienced CRS of grade 3 or higher. In the standard-risk B-cell ALL and an average risk of relapse subgroup, 3 (0.9%) and 4 (1.1%) patients experienced pancreatis of grade 3 or higher in the blinatumomab plus chemotherapy arm and chemotherapy arm, respectively. Patients in this subgroup experienced neurotoxic events of grade 3 or higher (seizure: 4 [1.1%] and 7 [1.9%]; all other CNS events: 2 [0.6%] and 3 [0.8%]; and peripheral neuropathy: 2 [0.6%] and 9 [2.4%] in the blinatumomab plus chemotherapy arm and chemotherapy arm, respectively). In the standard-risk B-cell ALL and a high risk of relapse subgroup, 11 (4.0%) and 8 (2.9%) of patients experienced pancreatis of grade 3 or higher in the blinatumomab plus chemotherapy arm and chemotherapy arm, respectively. Patients in this subgroup experienced neurotoxic events of grade 3 or higher (seizure: 10 [3.7%] and 7 [2.5%]; all other CNS events: 3 [1.1%] and 4 [1.4%]; peripheral neuropathy: 6 [2.2%] and 2 [0.7%] in the blinatumomab plus chemotherapy arm and chemotherapy arm, respectively].

Withdrawals Due to AEs

E1910 Trial

Withdrawals due to AEs were NR among the step 3 safety analysis set of the E1910 trial; however, they were available for the step 3 analysis set. Among patients included in the step 3 analysis set, 14 of 152 patients (9.2%) in the blinatumomab plus chemotherapy arm discontinued treatment due to AEs, side effects, or complications compared with 5 of 134 patients (3.7%) who discontinued due to AEs, side effects, or complications in the chemotherapy arm.

AALL1731 Trial

Withdrawals due to AEs in the AALL1731 trial were not provided in the materials reviewed by the CDA-AMC review team.

Treatment-Emergent SAEs

E1910 Trial

A higher percentage of patients in the blinatumomab plus chemotherapy arm of the step 3 safety analysis set in the E1910 trial experienced treatment-emergent SAEs (82 of 147; 55.8%) than in the chemotherapy arm (36 of 128; 28.1%). The 3 most common treatment-emergent SAEs in the blinatumomab plus chemotherapy arm were infections and infestations (22.4%), investigations (15.6%), and nervous system disorders (15.0%). In the chemotherapy arm, the 3 most common treatment-emergent SAEs were infections and infestations (14.8%), blood and lymphatic system disorders (11.7%), and investigations (4.7%).

AALL1731 Trial

Treatment-emergent SAEs in the AALL1731 trial were not provided in the materials reviewed by the CDA-AMC review team.

Fatal TEAEs

E1910 Trial

A similar percentage of patients in both treatment arms of the step 3 safety analysis set in the E1910 trial had a fatal TEAE (3 of 147 [2.0%] in the blinatumomab plus chemotherapy arm and 2 of 128 [1.6%] in the chemotherapy arm). In the blinatumomab plus chemotherapy arm, 2 of the fatal TEAEs were due to sepsis (1.4%) and 1 was due to intracranial hemorrhage (0.7%). In the chemotherapy arm, 1 of the fatal TEAEs was due to sepsis (0.8%) and 1 was due to cardiac arrest (0.8%).

AALL1731 Trial

Five patients in the AALL1731 trial had a fatal TEAE while in remission; all these patients were classified as having high risk of relapse. Two of the patients were in the chemotherapy arm (both deaths were sepsis-related) and 3 patients were in the blinatumomab plus chemotherapy arm (1 death was due to sepsis, 1 was due to multiorgan failure, and 1 was due to hypoxic ischemic encephalopathy). None of the deaths occurred during blinatumomab cycles.

Notable Harms

E1910 Trial

Among TEAEs of special interest identified in the blinatumomab product monograph and highlighted as important by the clinical experts consulted for this review, tumour lysis syndrome was NR for the step 3 safety analysis set in the E1910 trial. CRS occurred in a higher percentage of patients in the blinatumomab plus chemotherapy arm (23 of 147; 15.6%) than in the chemotherapy arm (0 of 128; 0.0%). Although infections were not stratified by severity, any infections and infestations occurred in a higher percentage of patients in the blinatumomab plus chemotherapy (34.7%) than in the chemotherapy arm (27.3%). However, most subcategories of infections of special interest were NR, including *Fusarium* infection, fungal pneumonia, septic shock, *Aspergillus* infection, bronchopneumonia, *Candida* infection, enterococcal bacteremia, *Escherichia* sepsis, and lung infection. Finally, relatively few patients in both the blinatumomab plus chemotherapy and chemotherapy treatment arms experienced neurotoxicity (2.4% versus 0.0%, respectively) or pancreatitis (0.0% and 0.8%, respectively).

AALL1731 Trial

Some of the TEAEs of special interest identified in the product monograph and highlighted as important by the clinical experts consulted for this review are covered in the reporting of grade 3 or higher TEAEs; however, data on notable harms of any grade were not available.

Critical Appraisal

The E1910 and AALL1731 trials were both randomized, open-label, phase III studies. The open-label nature of both studies poses a risk of bias from lack of blinding. The risk of bias due to lack of blinding is minimal for objective outcomes, such as OS; however, it remains for more subjectively assessed outcomes, such as RFS, DFS, and AEs. Although central laboratories reviewed and confirmed relapses in both studies to mitigate potential bias for RFS and DFS outcomes, assessment bias remains a risk for AEs.

Because none of the analyses in the E1910 and AALL1731 trials were adjusted for multiple testing, there is an increased risk of type I error for statistically significant results.

All results from the E1910 and AALL1731 trials should be interpreted with the understanding that these are based on interim analyses, which may overestimate the observed treatment effects for blinatumomab plus chemotherapy. Additionally, data from both trials remained immature (59 of 94 planned OS events had occurred in the FAS of the E1910 trial and 81 of 194 planned DFS events had occurred in the overall cohort of the AALL1731 trial). Nonetheless, because the clinical experts consulted for this review with experience treating patients with ALL felt the chemotherapy arms in both studies performed as expected, bias resulting from the interim analysis effect and immature data was deemed to be minimal. Further, OS results in the AALL1731 trial and OS and RFS results in the step 3 analysis set in the E1910 trial must be interpreted with the understandingthat these are from post hoc analyses which are at risk of data manipulation. However, the results of the post hoc analyses were consistent with those observed for primary and secondary outcomes as well as with the clinical expert’s expectations regarding the performance of the control and intervention arms.

The outcomes measured in the E1910 and AALL1731 trials addressed the key treatment goals identified by patient and clinician group input submitted to CDA-AMC and were deemed to be relevant by the consulted clinical experts.

E1910 Trial

As a result of a protocol amendment in the E1910 trial, patients with MRD positivity were assigned, rather than randomized, to the blinatumomab plus chemotherapy arm. This occurred as a result of updated evidence suggesting blinatumomab plus chemotherapy should be the new SOC for patients with MRD positivity. As a result, a higher percentage of patients in the blinatumomab plus chemotherapy arm had MRD positivity. Patients with MRD positivity have a higher chance of relapse; however, the direction and magnitude of this potential selection bias is unclear.

Baseline characteristics were generally similar in the step 3 analysis set and the FAS; however, the distribution of most characteristics were not similar for patients in the step 3 MRD-positive analysis set. The absence of randomization for the step 3 MRD-positive analysis set increases the risk of imbalance in measured and unmeasured confounders, although the magnitude and direction of the potential selection bias is hard to determine, as mentioned.

Stratified Cox proportional hazards models adjusted for stratification factors were used to estimate the HRs and CIs for OS and RFS. These models assume proportional hazards across treatment arms. Visual inspection of the KM curves by the CDA-AMC review team revealed the OS and RFS curves for the intervention and comparator treatment arms crossed multiple times and did not separate until approximately 4 and 6 months, respectively. Although this suggests that the HRs may not reflect the treatment effect over time, it is more likely a result of variation in effects between the treatment and an active control during the early stages of treatment initiation. The KM curves remained separate for the remainder of the observation period suggesting that the proportional hazards assumption was adequately met. Additionally, sensitivity analyses in the FAS using restricted mean survival time (RMST), which does not rely on the proportional hazards assumption, supported the results of the Cox proportional hazards models for OS and RFS.

The OS analysis in the step 3 analysis set, the FAS, and the step 3 MRD-positive analysis set indicated a survival benefit for the blinatumomab plus chemotherapy arm compared with the chemotherapy arm. However, its internal validity may have been influenced by the potential impact of postrelapse therapies. The OS analysis was based on the intention-to-treat (ITT) approach, which assumes postrelapse therapies are nondifferentially distributed between groups — a condition that may not hold given the observed disparities in postrelapse therapy use — and the OS analyses did not control or adjust for subsequent postrelapse therapy. Although this approach improves generalizability of the OS results, there is potential for confounding by postrelapse therapy, especially considering the noted differences in the use of efficacious postrelapse therapies. Although the observed OS effect represents the combined impact of front-line blinatumomab plus chemotherapy plus subsequent treatments, the overall effect of the differences in use of postrelapse therapy was more likely to favour the chemotherapy alone arm.

The clinical experts consulted for this review with experience treating adult patients with ALL noted that, in Canadian clinical practice, the modified Dana-Farber Cancer Institute (DFCI) protocol is currently the most

commonly used protocol to treat Ph-negative B-cell ALL. The chemotherapy regimen used in the E1910 trial is built upon the UKALLXII/E2993 chemotherapy regimen, with dosing modifications based on the C10403 AYA trial, and no indirect treatment comparison was submitted, thus limiting the generalizability to the Canadian setting. However, the clinical expert consulted for this review with experience treating adult patients with ALL felt the efficacy, based on CR and OS, of the regimen used in E1910 to be similar to the modified DFCI regimen.

AALL1731 Trial

Baseline characteristics were generally similar between the treatment arms in the AALL1731 trial, except for MRD in peripheral blood on day 8 in both the standard-risk B-cell ALL and an average risk and standard-risk B-cell ALL and a high risk of relapse subgroups and for the cytogenic risk group in the standard-risk B-cell ALL and a high risk of relapse subgroup. In the standard-risk B-cell ALL and an average risk and high risk of relapse strata, more patients in the blinatumomab plus chemotherapy arm (41.5% and 40.5%, respectively) than in the chemotherapy arm (35.2% and 35.2%, respectively) had 1% or greater MRD in their peripheral blood on day 8. A smaller percentage of patients with standard-risk B-cell ALL and a high risk of relapse in the blinatumomab plus chemotherapy arm had favourable cytogenetics compared with the chemotherapy arm (23.9% versus 31.6%, respectively), and a larger percentage had neutral cytogenetics (54.8% versus 48.7%, respectively). Both MRD and cytogenetic risk are well-established prognostic factors in ALL and influence treatment response and outcomes. The highlighted differences indicate that a larger percentage of patients in the blinatumomab plus chemotherapy arm would be at higher risk of relapse and reduced survival. These could contribute to bias in the comparative outcomes between the treatment arms, potentially favouring chemotherapy.

Among all randomized patients, more patients assigned to the blinatumomab plus chemotherapy arm did not start postconsolidation treatment (n = 55 for patients with standard-risk B-cell ALL and an average risk of relapse and n = 20 for patients with standard-risk B-cell ALL and a high risk of relapse) than in the chemotherapy arm (n = 27 for patients with standard-risk B-cell ALL and an average risk of relapse and n = 13 for patients with standard-risk B-cell ALL and a high risk of relapse). These patients were included in the ITT analyses, which are widely used in clinical trials to preserve randomization and provide an unbiased estimate of the treatment effect. The ability of ITT analyses to handle attrition bias depends on the context and the mechanisms of missing data. ITT analyses will typically produce unbiased treatment estimates in situations in which data are missing completely at random or missing at random if appropriate methods are used to impute missing data (e.g., multiple imputation). However, in the case of data missing not at random, the ITT analysis may produce biased estimates. It was reported for the study that substantial or informative missingness was neither anticipated nor planned for based on experience from a previous Children's Oncology Group ALL trial. However, this assumption may be unrealistic because the reasons for not initiating postconsolidation therapy vary across the risk strata and treatment groups, potentially leading to data that are not missing at random. Without additional information or results from analyses to determine whether data were missing not at random, it is not possible to determine the impact of attrition bias, if any. No data on treatment completion, discontinuation, dose modifications, or the use of off-protocol treatments were

submitted to CDA-AMC for review. Therefore, a comprehensive assessment of attrition and adherence and their potential impact on outcomes could not be done.

The AALL1731 trial planned to use stratified Cox proportional hazards models, adjusted for stratification factors, to test DFS. Tests of the proportional hazards assumption, including the Schoenfeld residuals test (P = 0.031), a Wald test of time-varying interaction (P = 0.048), and a Kolmogorov-type supremum test (P = 0.068), suggested the assumption may not hold. Visual inspection of the KM curves showed no converging or crossing of the DFS curves, but indicated the treatment effect could have a delay of approximately 2 months before achieving a separation of the curves. In a sensitivity analysis, DFS was analyzed using the RMST method, an appropriate alternative survival analysis approach that does not rely on the proportional hazards assumption. Results for the RMST method, which does not rely on the proportional hazards assumption, supported the results of the Cox proportional hazards model for DFS.

Data completeness and transparency of reporting were limitations of the AALL1731 trial. Detailed patient disposition among randomized patients, the receipt of on-protocol and off-protocol therapy, any TEAEs, withdrawals due to AEs, treatment-emergent SAEs, and notable harms were NR.

External Validity

Although the comparators in the E1910 and AALL1731 trials were deemed to be acceptable by the clinical experts consulted for this review, blinatumomab is already publicly reimbursed for patients who are MRD-positive (per PC0204 CADTH Reimbursement Review). No direct or indirect evidence was provided assessing the comparative efficacy of blinatumomab between the currently funded indication and the indication under review. The clinical experts consulted for this review indicated that, for patients with MRD positivity, it is expected that blinatumomab has similar efficacy per the currently funded indication and the indication under review. According to the clinicians consulted for this review, clinicians would likely prefer prescribing blinatumomab per the current review because it can be combined with chemotherapy and does not require completion of 3 intensive chemotherapy blocks. In addition, the clinical experts consulted for this review noted that the current review of blinatumomab adds value for patients who have lower levels of MRD (MRD of 0.01% to < 0.1%; an estimated 5% to 10% of patients as per the clinical experts) and who are excluded from the currently funded blinatumomab indication. However, in situations in which pediatric patients cannot tolerate additional cycles of consolidation chemotherapy, blinatumomab per the current funded indication allows for multiple treatment cycles of blinatumomab to manage leukemia without requiring alternating treatment with consolidation chemotherapy. According to the clinical experts, the choice between both blinatumomab indications should be left to the treating clinician and the patient.

The evidence under review was restricted to a narrower population than the reimbursement request:

- Age groups (E1910 and AALL1731 trials) — Although both trials restricted enrolment based on age (aged 30 to 70 years in the E1910 trial and aged 1 year to < 10 years in the AALL1731 trial), the clinical experts consulted for this review felt the results of the AALL1731 trial could be generalized to those younger than 1 year and between 10 and 18 years while the results of the E1910 trial could be generalized to those aged between 18 and 30 years and older than 70 years.

- Risk groups (AALL1731 trial) — The AALL1731 trial results were restricted to patients with standard-risk B-cell ALL (defined as patients aged 1 year to < 10 years at diagnosis and a white cell count of < 50,000/μL) with an average or high risk of relapse after induction therapy. The clinical expert consulted for this review with experience treating pediatric patients with ALL noted that the definition of standard-risk B-cell ALL is well established and they felt the results among the cohort with standard-risk B-cell ALL and high risk of relapse could be generalized to patients with high-risk and very high–risk B-cell ALL. Although no data were available for the cohort with a favourable risk of relapse, the clinical expert noted that these patients may not require treatment with blinatumomab because the efficacy of chemotherapy in these patients is high. However, the clinical expert consulted for this review felt the decision to treat pediatric patients with a standard-risk B-cell ALL and a favourable risk of relapse should be left up to the treating physician.
- MRD status (AALL1731 trial) — Patients with standard-risk B-cell ALL and a high risk of relapse after induction therapy who had MRD of 0.1% or greater were reassessed for MRD at the end of consolidation, which is common practice according to the clinical expert with experience treating pediatric patients. Patients with end-of-consolidation MRD of less than 0.1% were randomized; those with MRD of 0.1% to less than 1.0% (n = 14) were nonrandomly assigned to receive blinatumomab plus chemotherapy (results are not available), and those with MRD greater than 1% (n = 7) were removed from the trial. The clinical expert with experience treating children agreed to generalize the results of patients with standard-risk B-cell ALL and a high risk of relapse and MRD of less than 0.1% at the end of consolidation to patients with MRD of 0.1% to less than 1.0%. The clinical expert with experience treating children noted that the patient population with standard-risk B-cell ALL and a high risk of relapse and end-of-consolidation MRD of 1% or greater (n = 7) was removed from the trial because these patients reflect a rare and very high–risk subgroup that is considered refractory and would be managed differently.

GRADE Summary of Findings and 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 inform 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.

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. Although literature-based thresholds were unavailable for the current review, the clinical experts consulted for this review provided estimates for clinically meaningful thresholds for all outcomes assessed using GRADE.

Findings from the E1910 trial were included in the GRADE assessments. Results from the AALL1731 trial were not appraised using GRADE because only published results, not a formal Clinical Study Report, was provided to CDA-AMC and the data were based on public sources.

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:

- OS (probabilities at 3 and 5 years) and RFS (probabilities at 1, 3, and 5 years) in the overall population (i.e., regardless of MRD status) and in MRD-negative and MRD-positive populations
- harms (any grade 3 or higher TEAEs, treatment-emergent SAEs, and fatal AEs) in the overall population.

Table 3 presents the GRADE summary of findings for blinatumomab plus chemotherapy versus chemotherapy for adult patients with Ph-negative B-cell ALL.

Table 3: Summary of Findings for Blinatumomab Plus Chemotherapy Versus Chemotherapy for Adults With Ph-Negative CD19-Positive B-cell ALL

Outcome, population, and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Chemotherapy	Blinatumomab + chemotherapy	Difference		
Overall survival							
Probability of OS at 3 years							
Step 3 analysis set[a] (MRD-negative and MRD-positive groups) Follow-up: median = 4.5 years in both treatment arms[b]	286 (1 RCT)	NR	65.7 per 100	82.6 per 100 (75.5 per 100 to 87.8 per 100)	16.9 more per 100 (5.5 more per 100 to 28.3 more per 100)	High[c,d]	Blinatumomab plus chemotherapy results in a clinically important increase in the probability of being alive at 3 years compared with chemotherapy alone.
Full analysis set[e] (MRD-negative group) Follow-up: median = 4.5 years in both treatment arms[b]	224 (1 RCT)	NR	70.0 per 100	85.5 per 100 (77.5 per 100 to 90.9 per 100)	15.6 more per 100 (3.0 more per 100 to 28.2 more per 100)	Moderate[c,f]	Blinatumomab plus chemotherapy likely results in a clinically important increase in the probability of being alive at 3 years compared with chemotherapy alone in patients with MRD negativity .
Step 3 MRD-positive analysis set[g] (MRD-positive group) Follow-up: median = 4.6 years in blinatumomab arm and median = 5.0 years in chemotherapy alone arm[b]	62 (1 RCT)	NR	43.2 per 100	74.2 per 100 (57.4 per 100 to 85.2 per 100)	31.1 more per 100 (4.1 more per 100 to 58.0 more per 100)	Moderate[c,h]	Blinatumomab plus chemotherapy likely results in a clinically important increase in the probability of being alive at 3 years compared with chemotherapy alone in patients with MRD positivity.
Probability of OS at 5 years							

Outcome, population, and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Chemotherapy	Blinatumomab + chemotherapy	Difference		
Step 3 analysis set[a] (MRD-negative and MRD-positive groups) Follow-up: median = 4.5 years in both treatment arms[b]	286 (1 RCT)	NR	58.3 per 100	79.1 per 100 (71.4 per 100 to 85.0 per 100)	20.8 more per 100 (8.5 more per 100 to 33.0 more per 100)	High[c,d]	Blinatumomab plus chemotherapy results in a clinically important increase in the probability of being alive at 5 years compared with chemotherapy alone.
Full analysis set[e] (MRD-negative group) Follow-up: median = 4.5 years in both treatment arms[b]	224 (1 RCT)	NR	62.5 per 100	82.4 per 100 (73.7 per 100 to 88.4 per 100)	19.9 more per 100 (6.3 more per 100 to 33.5 more per 100)	High[c,i]	Blinatumomab plus chemotherapy results in a clinically important increase in the probability of being alive at 5 years compared with chemotherapy alone in patients with MRD negativity.
Step 3 MRD-positive analysis set[g] (MRD-positive group) Follow-up: median = 4.6 years in blinatumomab arm and median = 5.0 years in chemotherapy alone arm[b]	62 (1 RCT)	NR	37.8 per 100	70.1 per 100 (52.0 per 100 to 82.5 per 100)	32.3 more per 100 (5.4 more per 100 to 59.3 more per 100)	High[c,j]	Blinatumomab plus chemotherapy results in a clinically important increase in the probability of being alive at 5 years compared with chemotherapy in patients with MRD positivity.
Relapse-free survival							
Probability of RFS at 1 year							
Step 3 analysis set[a] (MRD-negative and MRD-positive groups) Follow-up: median = 4.5 years in both treatment arms[b]	286 (1 RCT)	NR	75.8 per 100	88.0 per 100 (81.7 per 100 to 92.3 per 100)	12.2 more per 100 (1.8 more per 100 to 22.7 more per 100)	Moderate[c,k]	Blinatumomab plus chemotherapy likely results in a clinically important increase in the probability of being relapse-free at

Outcome, population, and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Chemotherapy	Blinatumomab + chemotherapy	Difference		
							1 year compared with chemotherapy alone.
Full analysis set[e] (MRD-negative group) Follow-up: median = 4.5 years in both treatment arms[b]	224 (1 RCT)	NR	81.9 per 100	90.1 per 100 (82.8 per 100 to 94.4 per 100)	8.2 more per 100 (3.0 less per 100 to 19.4 more per 100)	Moderate[c,l]	Blinatumomab plus chemotherapy likely results in a clinically important increase in the probability of being relapse-free at 1 year compared with chemotherapy alone in patients with MRD negativity.
Step 3 MRD-positive analysis set[g] (MRD-positive group) Follow-up: median = 4.6 years in blinatumomab arm and median = 5.0 years in chemotherapy alone arm[b]	62 (1 RCT)	NR	44.3 per 100	82.4 per 100 (66.5 per 100 to 91.2 per 100)	38.0 more per 100 (11.6 more per 100 to 64.5 more per 100)	High[c,m]	Blinatumomab plus chemotherapy results in a clinically important increase in the probability of being relapse-free at 1 year compared with chemotherapy in patients with MRD positivity.
Probability of RFS at 3 years							
Step 3 analysis set[a] (MRD-negative and MRD-positive groups) Follow-up: median = 4.5 years in both treatment arms[b]	286 (1 RCT)	NR	61.4 per 100	78.7 per 100 (71.2 per 100 to 84.4 per 100)	17.3 more per 100 (5.6 more per 100 to 28.9 more per 100)	High[c,n]	Blinatumomab plus chemotherapy results in a clinically important increase in the probability of being relapse-free at 3 years compared with chemotherapy alone.
Full analysis set[e] (MRD-negative group) Follow-up: median = 4.5 years in both treatment arms[b]	224 (1 RCT)	NR	65.7 per 100	81.1 per 100 (72.5 per 100 to 87.2 per 100)	15.4 more per 100 (2.3 more per 100 to 28.4 more per 100)	Moderate[c,l]	Blinatumomab plus chemotherapy likely results in a clinically important increase in the probability of

Outcome, population, and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Chemotherapy	Blinatumomab + chemotherapy	Difference		
							being relapse-free at 3 years compared with chemotherapy alone in patients with MRD negativity.
Step 3 MRD-positive analysis set[g] (MRD-positive group) Follow-up: median = 4.6 years in blinatumomab arm and median 5.0 = years in chemotherapy alone arm[b]	62 (1 RCT)	NR	39.4 per 100	71.8 per 100 (54.8 per 100 to 83.3 per 100)	32.4 more per 100 (6.1 more per 100 to 58.7 more per 100)	High[c,o]	Blinatumomab plus chemotherapy results in a clinically important increase in the probability of being relapse-free at 3 years compared with chemotherapy in patients with MRD positivity.
Probability of RFS at 5 years							
Step 3 analysis set[a] (MRD-negative and MRD-positive groups) Follow-up: median = 4.5 years in both treatment arms[b]	286 (1 RCT)	NR	57.2 per 100	75.6 per 100 (67.8 per 100 to 81.8 per 100)	18.4 more per 100 (6.3 more per 100 to 30.6 more per 100)	High[c,n]	Blinatumomab plus chemotherapy results in a clinically important increase in the probability of being relapse-free at 5 years compared with chemotherapy alone.
Full analysis set[e] (MRD-negative group) Follow-up: median = 4.5 years in both treatment arms[b]	224 (1 RCT)	NR	60.5 per 100	77.0 per 100 (67.8 per 100 to 83.8 per 100)	16.5 more per 100 (2.6 more per 100 to 30.3 more per 100)	Moderate[c,l]	Blinatumomab plus chemotherapy likely results in a clinically important increase in the probability of being relapse-free at 5 years compared with chemotherapy alone in patients with MRD negativity.

Outcome, population, and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Chemotherapy	Blinatumomab + chemotherapy	Difference		
Step 3 MRD-positive analysis set[g] (MRD-positive group) Follow-up: median = 4.6 years in blinatumomab arm and median = 5.0 years in chemotherapy alone arm[b]	62 (1 RCT)	NR	39.4 per 100	71.8 per 100 (54.8 per 100 to 83.3 per 100)	32.4 more per 100 (6.1 more per 100 to 58.7 more per 100)	High[c,o]	Blinatumomab plus chemotherapy results in a clinically important increase in the probability of being relapse-free at 3 years compared with chemotherapy alone in patients with MRD positivity.
Harms							
Incidence of any grade 3 or higher TEAE Step 3 safety analysis set[p] (MRD-negative and MRD-positive groups) Follow-up: DCO by June 23, 2023	275 (1 RCT)	NR	97.7 per 100	95.9 per 100	1.74 less per 100 (5.87 less per 100 to 2.40 more per 100)	Moderate[c,q]	Blinatumomab plus chemotherapy likely results in little to no difference in the incidence of any grade 3 or higher TEAE compared with chemotherapy alone.
Incidence of treatment-emergent SAE Step 3 Safety analysis set[p] (MRD-negative and MRD-positive groups) Follow-up: DCO by June 23, 2023	275 (1 RCT)	NR	28.1 per 100	55.8 per 100	27.66 more per 100 (16.47 more per 100 to 38.84 more per 100)	Moderate[c,r]	Blinatumomab plus chemotherapy likely results in a clinically important increase in the incidence of treatment-emergent SAEs compared with chemotherapy alone.
Incidence of fatal TEAEs Step 3 safety analysis set[p] (MRD-negative and MRD-positive groups) Follow-up: DCO by June 23, 2023	275 (1 RCT)	NR	1.6 per 100	2.0 per 100	0.48 more per 100 (2.66 less per 100 to 3.62 more per 100)	Very low[c,s]	The evidence is very uncertain about the effect of blinatumomab plus chemotherapy on fatal TEAEs compared with chemotherapy alone.

CI = confidence interval; DCO = data cut-off; KM = Kaplan-Meier; MRD = minimal residual disease; NR = not reported; OS = overall survival; Ph = Philadelphia chromosome; RCT = randomized controlled trial; RFS = relapse-free survival; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

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

[a]Step 3 analysis set: All 286 step 3 randomized or registered patients combined regardless of MRD status (152 patients in the blinatumomab plus chemotherapy arm and 134 patients in the chemotherapy arm).

[b]Estimated via median time to KM censoring.

[c]The between-group difference in survival probability was requested from the sponsor to aid in the interpretation of the results for this end point.

[d]Certainty was not rated down for indirectness or imprecision. Although limitations regarding internal validity were identified (open-label design, potential selection bias, results from interim analyses, and OS was conducted as a post hoc analysis), certainty was not rated down for risk of bias because the limitations were determined to have a small or no impact on the results. No empirically derived and validated minimal important difference (MID) was identified for the between-group difference in the probability of survival. The clinical experts consulted for this review suggested that a 5% between-group difference would be clinically meaningful, and this value was used as the threshold.

[e]Full analysis set: All 224 step 3 randomized patients who were assessed as MRD-negative centrally after induction and intensification chemotherapy (112 patients in the blinatumomab plus chemotherapy arm and 112 patients in the chemotherapy arm).

[f]Certainty was not rated down for indirectness. Although limitations regarding internal validity were identified (open-label design, results from interim analyses, and OS was conducted as a post hoc analysis), certainty was not rated down for risk of bias because the limitations were determined to have a small or no impact on the results. Rated down 1 level for imprecision. No empirically derived and validated MID was identified for the between-group difference in the probability of survival. The clinical experts consulted for this review suggested that a 5% between-group difference would be clinically meaningful, and this value was used as the threshold. The point estimate suggests clinically meaningful increases in OS at 3 years while the lower bound of the 95% CI crosses the between-group difference threshold of 5%.

[g]Step 3 MRD-positive analysis set: All 62 patients from the step 3 analysis set with MRD positivity at step 3 using the protocol-specified cut-off of ≤ 0.01% (40 patients in the blinatumomab plus chemotherapy arm and 22 patients in the chemotherapy arm).

[h]Certainty was not rated down for indirectness. Although limitations regarding internal validity were identified (open-label design, potential selection bias, results from interim analyses, and OS was conducted as a post hoc analysis), certainty was not rated down for risk of bias because the limitations were determined to have a small or no impact on the results. Rated down 1 level for imprecision. No empirically derived and validated MID was identified for the between-group difference in the probability of survival. The clinical experts consulted for this review suggested that a 5% between-group difference would be clinically meaningful, and this value was used as the threshold. The point estimate suggests clinically meaningful increases in OS at 3 years while the lower bound of the 95% CI crosses the between-group difference threshold of 5%. Although results are from a relatively small sample (n = 62), certainty was not further rated down due to imprecision because this limitation was determined to have a small or no impact on the results.

[i]Certainty was not rated down for indirectness or imprecision. Although limitations regarding internal validity were identified (open-label design, results from interim analyses, and OS was conducted as a post hoc analysis), certainty was not rated down for risk of bias because the limitations were determined to have a small or no impact on the results. No empirically derived and validated MID was identified for the between-group difference in the probability of survival. The clinical experts consulted for this review suggested that a 5% between-group difference would be clinically meaningful, and this value was used as the threshold.

[j]Certainty was not rated down for indirectness. Although limitations regarding internal validity were identified (open-label design, potential selection bias, results from interim analyses, and OS was conducted as a post hoc analysis), certainty was not rated down for risk of bias because the limitations were determined to have a small or no impact on the results. Although results are from a relatively small sample (n = 62), certainty was not rated down due to imprecision because the limitations were determined to have a small or no impact on the results. No empirically derived and validated MID was identified for the between-group difference in the probability of survival. The clinical experts consulted for this review suggested that a 5% between-group difference would be clinically meaningful, and this value was used as the threshold.

[k]Certainty was not rated down for indirectness. Although limitations regarding internal validity were identified (open-label design, potential selection bias, and results from interim analyses), certainty was not rated down for risk of bias because the limitations were determined to have a small or no impact on the results. No empirically derived and validated MID was identified for the between-group difference in the probability of remaining relapse-free. The clinical experts consulted for this review suggested that a 5% to 7% between-group difference would be clinically meaningful, and this range was used as the threshold. Rated down 1 level for imprecision. The point estimate suggests clinically meaningful increases in RFS at 1 year while the lower bound of the 95% CI crosses the between-group difference threshold of 5% to 7%.

[l]Certainty was not rated down for indirectness. Although limitations regarding internal validity were identified (open-label design and results from interim analyses), certainty was not rated down for risk of bias because the limitations were determined to have a small or no impact on the results. No empirically derived and validated MID was identified for the between-group difference in the probability of remaining relapse-free. The clinical experts consulted for this review suggested that a 5% to 10% between-group difference would be clinically meaningful, and this range was used as the threshold. Rated down 1 level for imprecision. The point estimate suggests clinically meaningful increases in RFS at 1, 3, and 5 years while the lower bound of the 95% CI crosses the between-group difference threshold of 5% to 10%.

[m]Certainty was not rated down for indirectness. Although limitations regarding internal validity were identified (open-label design, potential selection bias, and results from interim analyses), certainty was not rated down for risk of bias because the limitations were determined to have a small or no impact on the results. No empirically derived and validated MID was identified for the between-group difference in the probability of remaining relapse-free. The clinical experts consulted for this review suggested that a 5% to 10% between-group difference would be clinically meaningful, and this range was used as the threshold. Although results are from a relatively small sample (n = 62), certainty was not rated down due to imprecision because this limitation was determined to have a small or no impact on the results.

[n]Certainty was not rated down for indirectness. Although limitations regarding internal validity were identified (open-label design, potential selection bias, and results from interim analyses), certainty was not rated down for risk of bias because the limitations were determined to have a small or no impact on the results. No empirically derived and validated MID was identified for the between-group difference in the probability of remaining relapse-free. The clinical experts consulted for this review suggested that a 5% to 7% between-group difference would be clinically meaningful, and this range was used as the threshold. The point estimate and upper bound of the 95% CI suggests

clinically meaningful increases in RFS at 3 and 5 years. The lower bound of the 95% CI is greater than the lower limit of the between-group difference threshold (5%) and thus certainty was not rated down; however, if the upper limit of the threshold (7%) is used, certainty would be rated down due to imprecision.

[o]Certainty was not rated down for indirectness. Although limitations regarding internal validity were identified (open-label design, potential selection bias, and results from interim analyses), certainty was not rated down for risk of bias because the limitations were determined to have a small or no impact on the results. No empirically derived and validated MID was identified for the between-group difference in the probability of remaining relapse-free. The clinical experts consulted for this review suggested that a 5% to 10% between-group difference would be clinically meaningful, and this range was used as the threshold. The point estimate and upper bound of the 95% CI suggests clinically meaningful increases in RFS at 3 and 5 years. The lower bound of the 95% CI is greater than the lower limit of the between-group difference threshold (5%) and thus certainty was not rated down; however, if the upper limit of the threshold (10%) is used, certainty would be rated down due to imprecision. Although results are from a relatively small sample (n = 62), certainty was not rated down due to imprecision because this limitation was determined to have a small or no impact on the results.

[p]Step 3 safety analysis set: All 275 patients in the step 3 analysis set who had at least 1 dose of protocol-specified therapies (147 patients in the blinatumomab plus chemotherapy arm and 128 patients in the chemotherapy arm).

[q]Certainty was not rated down for indirectness or imprecision. Rated down 1 level for risk of bias. Due to the open-label nature of the study, there is substantial risk of bias for subjective outcomes. No empirically derived and validated MID was identified for the between-group difference in the incidence of any grade 3 or greater TEAE. The clinical experts consulted for this review suggested that a 10% between-group difference would be clinically meaningful, and this value was used as the threshold.

[r]Certainty was not rated down for indirectness or imprecision. Rated down 1 level for risk of bias. Due to the open-label nature of the study, there is substantial risk of bias for subjective outcomes. No empirically derived and validated MID was identified for the between-group difference in the incidence of treatment-emergent SAE. The clinical experts consulted for this review suggested that a 10% to 15% between-group difference would be clinically meaningful, and this range was used as the threshold.

[s]Certainty was not rated down for indirectness. Rated down 1 level for risk of bias. Due to the open-label nature of the study, there is substantial risk of bias for subjective outcomes. Rated down 2 levels for imprecision. No empirically derived and validated MID was identified for the between-group difference in the incidence of fatal TEAEs. The clinical experts consulted for this review suggested that a greater than 0% between-group difference would be clinically meaningful, and this value was used as the threshold. The point estimate suggests clinically meaningful increases in fatal TEAEs while the upper and lower bounds of the 95% CI cross the between-group difference threshold of 0% suggested by clinical experts. Given the small number of events, there is substantial uncertainty in the between-group difference.

Source: Blincyto Clinical Study Report. Details included in the table are from the sponsor's Summary of Clinical Evidence.

Long-Term Extension Studies

No long-term extension studies were submitted.

Indirect Comparisons

No indirect evidence was submitted.

Studies Addressing Gaps in the Evidence From the Systematic Review

No additional studies to address gaps within the systematic review evidence were submitted.

Economic Evidence

Cost and Cost-Effectiveness

Table 4: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Partitioned survival with a mixture cure component for adult patients; partitioned survival model for pediatric patients
Target population	Adult and pediatric patients with Ph-negative, CD19-positive B-cell ALL in the consolidation phase of multiphase chemotherapy in front-line setting
Treatment	Blinatumomab in combination with SOC
Dose regimen	A single cycle of blinatumomab treatment is 28 days of continuous infusion followed by a 14-day treatment-free interval. Dose: 28 mcg/day for patients weighing 45 kg or more; 15 mcg/m^2 per day based on body surface area (not to exceed 28 mcg/day) for patients weighing less than 45 kg.
Submitted price	Blinatumomab: $2,978.26 per 38.5-mcg vial
Submitted treatment cost	$83,391 per cycle for adult patients; $46,289 per cycle for pediatric patients
Comparators	Adult SOC: A multiagent chemotherapy consisting of daunorubicin, vincristine, methotrexate, cyclophosphamide, cytarabine, etoposide, pegaspargase, dexamethasone, and 6-mercaptopurine Pediatric SOC: Varied by standard-risk group and may include vincristine, methotrexate, dexamethasone, pegaspargase, mercaptopurine, leucovorin, doxorubicin, cyclophosphamide, thioguanine, and cytarabine
Perspective	Canadian publicly funded health care payer
Outcomes	Life-years, QALYs
Time horizon	Lifetime (50 years for adult patients and 92 years for pediatric patients)
Key data sources	E1910 trial to inform the adult model AALL1731 trial to inform the pediatric model

Component	Description
Key limitations	• The long-term comparative efficacy of blinatumomab plus SOC compared with SOC alone is uncertain. Parametric survival functions were used to extrapolate the KM curves over the time horizon of the model in the adult population, and most of the incremental QALYs associated with blinatumomab plus SOC were projected during the extrapolated period, which contributes to the uncertainty of the long-term clinical benefits. • For the pediatric population, the sponsor used KM data directly for the first 4 years of the modelled time horizon without conducting survival analysis for DFS and OS. This approach was inappropriate and did not incorporate parameter uncertainty. Further, visual inspection of the OS KM curves suggested little difference between the blinatumomab plus SOC arm and SOC alone arm. The submitted model was not programmed to account for such uncertainty; as a result, it is not possible to establish the impact of this uncertainty on the results of the model. • Clinical experts consulted by CDA-AMC suggested that the inpatient days for pediatric patients in both relapse-free and postrelapse health states, as well as for adult patients in the relapse-free health state, were likely overestimated. • For the drug acquisition costs in the adult population, the sponsor assumed 100% RDI for SOC in both arms, which may have overestimated the cost of SOC, when applying RDI observed in the E1910 trial for blinatumomab. • Poor modelling practices were employed, including extensive use of IFERROR statements that overwrite parameter values, incorrect cell referencing for calculating HCRU costs and utility decrement for blinatumomab treatments, and limited flexibility for user input on key parameters.
CDA-AMC reanalysis results	• In the CDA-AMC base case, no OS benefit for blinatumomab in a pediatric population was assumed, the inpatient hospitalization days in both populations were adjusted, and the RDIs obtained from the E1910 trial for SOC in an adult population were applied. • Based on the CDA-AMC base case, blinatumomab plus SOC was associated with an ICER of $37,111 per QALY gained (incremental costs = $95,728; incremental QALYs = 2.58) compared with SOC alone.

ALL = acute lymphoblastic leukemia; CDA-AMC = Canada's Drug Agency; DFS = disease-free survival; HCRU = health care resource utilization; ICER = incremental cost-effectiveness ratio; KM = Kaplan-Meier; OS = overall survival; Ph = Philadelphia chromosome; QALY = quality-adjusted life-year; RDI = relative dose intensity; SOC = standard of care.

Budget Impact

CDA-AMC identified the following key limitations with the sponsor's analysis: the comparator does not reflect Canadian clinical practice, postrelapse hematopoietic SCT costs were inaccurately calculated, the market uptake of blinatumomab plus SOC was likely underestimated in the pediatric population, the average annual percentage change in ALL incidence was likely overestimated, the methodology to model OS for the pediatric population was inappropriate and associated with uncertainty, and use of relative dose intensity to estimate actual drug costs is not appropriate. Based on the CDA-AMC reanalysis, the 3-year budget impact of funding blinatumomab as part of consolidation therapy in adult and pediatric patients with Ph-negative, CD19-positive B-cell ALL in the consolidation phase of multiphase chemotherapy in the front-line setting is $102,505,910 (year 1 = $31,603,539; year 2 = $34,583,830; year 3 = $36,318,540). For adult and pediatric populations, the budget impact is estimated to be $66,257,182 and $36,248,727 over the 3-year time horizon, respectively.

pERC Information

Members of the Committee

Dr. Catherine Moltzan (Chair), Dr. Phillip Blanchette, Dr. Kelvin Chan, Dr. Matthew Cheung, Dr. Michael Crump, Annette Cyr, Dr. Jennifer Fishman, Dr. Jason Hart, Terry Hawrysh, Dr. Yoo-Joung Ko, Dr. Aly-Khan Lalani, Amy Peasgood, Dr. Anca Prica, Dr. Adam Raymakers, Dr. Patricia Tang, Dr. Pierre Villeneuve, and Danica Wasney.

Meeting date: March 5, 2025

Regrets: Three expert committee members did not attend.

Conflicts of interest: None

Canada's Drug Agency
L'Agence des médicaments du Canada
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Questions or requests for information about this report can be directed to Requests@CDA-AMC.ca.