Canada's Drug Agency
L'Agence des médicaments du Canada

CDA-AMC REIMBURSEMENT REVIEW

Patient and Clinician Group Input

blinatumomab (Blincyto)

(Amgen Canada Inc.)

Indication: For the treatment of adult and pediatric patients with Philadelphia chromosome-negative CD19 positive B-cell precursor acute lymphoblastic leukemia in the consolidation phase of multiphase chemotherapy in the frontline setting.

November 25, 2024

This document compiles the input submitted by patient groups and clinician groups for the file under review. The information is used by CDA-AMC in all phases of the review, including the appraisal of evidence and interpretation of the results. The input submitted for each review is also included in the briefing materials that are sent to expert committee members prior to committee meetings. **If your group has submitted input that is not reflected within this document, please contact Formulary-Support@cda-amc.ca.**

Disclaimer: The views expressed in this submission are those of the submitting organization or individual. As such, they are independent of CDA-AMC and do not necessarily represent or reflect the views of CDA-AMC. No endorsement by CDA-AMC is intended or should be inferred.

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CDA-AMC does use reasonable care to prevent disclosure of personal information in posted material; however, it is ultimately the submitter's responsibility to ensure no identifying personal information or personal health information is included in the submission. The name of the submitting group and all conflicts of interest information from individuals who contributed to the

CADTH

Patient Input Template for CADTH Reimbursement Reviews

Name of Drug: 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.
Name of Patient Group: The Leukemia & Lymphoma Society of Canada

1. About Your Patient Group

The Leukemia & Lymphoma Society of Canada (LLSC) - bloodcancers.ca

LLSC is a national charitable status organization dedicated to finding a cure for blood cancers and its ability to improve the quality of life of people affected by blood cancers and their families by funding life-enhancing research and providing educational resources, services, and support. The Leukemia and Lymphoma Society of Canada is the largest charitable organization in Canada dedicated to blood cancer, our focus includes:

- Funding research from bench to bedside.
- Rethinking how a person navigates their blood cancer experience
- Providing targeted blood cancer information
- Offering tools for psychological and emotional support
- Empowering Canadians to take charge of their blood cancer experience through practical support and advocacy

2. Information Gathering

One online survey was created through SurveyMonkey. This survey asked for information and insights regarding experiences of adults diagnosed with ALL and their caregivers. Information was gathered in October and November 2024. The survey was developed and distributed by LLSC, in English only. The survey was distributed through various social media channels and directly by email.

110 respondents participated in this survey. The majority of respondents (68.51%) indicated that they were the ALL patient (past or present). 27.78% of respondents indicated that they were a caregiver of an ALL patient (past or present). 4 respondents answered “other” and were disqualified from the survey.

Respondents were asked to identify the age range of the person diagnosed with ALL at the time of diagnosis. 9/103 (8.74%) answered 0-17 years and were disqualified from the survey.

50/103 (48.54%) answered 18-39
33/103 (32.04%) answered 40-64
8/103 (7.77%) answered 65-74
3/103 (2.91%) answered 75+
93 respondents identified their primary residence:

Ontario (40), British Columbia (20) Nova Scotia and Alberta (7 in each province), Newfoundland and Labrador (6), Prince Edward Island, Quebec, and Saskatchewan (3 in each province), New Brunswick (1), Northwest Territories (1). 1 respondent was from the USA and 1 respondent was International.

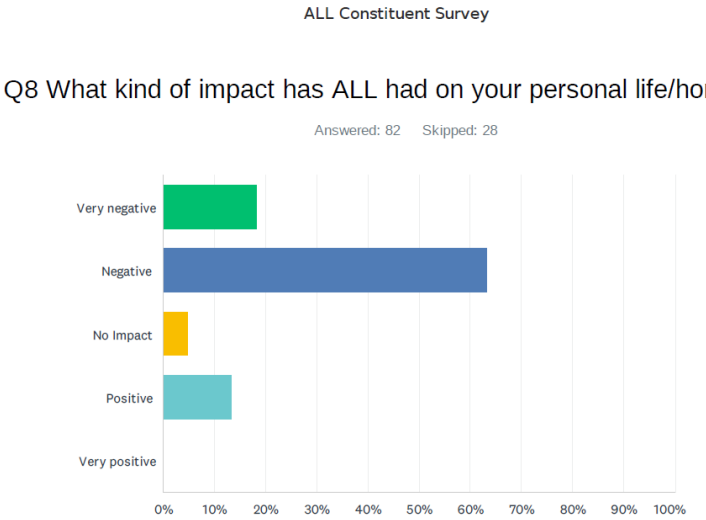
18/82 (21.95%) respondents stated that they or the person they care(d) for were treated with blinatumomab for ALL

3. Disease Experience

CADTH involves clinical experts in every review to explain disease progression and treatment goals. Here we are interested in understanding the illness from a patient's perspective. Describe how the disease impacts patients' and caregivers' day-to-day life and quality of life. Are there any aspects of the illness that are more important to control than others?

ALL had a significant negative impact on quality of life.

Respondents were asked, What kind of impact has ALL had on your **personal life/home life**? 82 respondents answered this question. 67/82 (81.70%) answered that ALL had a negative to very negative impact on the personal life/home life.



Some of the survey respondents elaborated:

- "I was diagnosed during the pandemic; it caused my husband and I to live apart. It instilled so much fear that we are not at all the couple we were before. My husband remains terrified day to day and when we were given the all-clear to co habitat again we still don't even sleep in the same bed"
- "My family doesn't socialize anymore for fear of catching a virus and making me ill. We don't go to large gatherings, and we mask at stores if we do go out. We can't ever be too far from home so that I can rest throughout the day. My husband has had to take on a caregiving role and handle more of the cooking/cleaning."
- "I couldn't see friends or family (I especially missed seeing my 2 grandkids - who were in daycare at the time - they weren't allowed on the Hematology floor) while undergoing the high intensity chemotherapy and then in rehab."

- “This is specific to my current age as peers are all having kids now and ALL left me infertile, so it is taking longer for us to explore alternate family planning options. So feeling a little left behind.”

ALL also had a significant negative impact on social life

Respondents were asked, What kind of impact has ALL had on your **social life**? 81 respondents answered this question. 61/81 (75.31%) answered that ALL had a negative to very negative impact on their social life:

- “It's very hard to see my friends and others my age move on in life like going to college, while I can't because I'm too sick. It's also frustrating to not be able to go party while I'm 20.”
- “Had to completely stop living our life - work, sports, leisure everything.”
- “I have very few friends as I still suffer from fatigue.”
- “Three years post-treatment, our social life has dwindled significantly. We transitioned from a vibrant social life with an extensive circle of friends to a more confined social sphere with fewer interactions. Many cannot comprehend or relate to the journey of cancer survivorship and its profound effects on one's identity and lifestyle after treatment. It alters priorities and the way you choose to live when life expectancy is uncertain. I harbor immense guilt over the toll this has taken on my husband, who was once a carefree spirit flourishing on social engagement.”
- “At first I had my closest friends reach out and send me care packages but as time has gone on I hear from friends less and less. They used to offer to visit and I had the energy in the beginning for an hour visit but now I don’t have the energy for anyone other than my husband and kids, so I don’t see visitors anymore. It’s also cold and flu season and it seems as though someone is always sick. It’s all very isolating.”
- “I isolated for so long I lost most of my former friends. I no longer work so lost my work friends. And I don't have the energy to do much by way of activities, so find it challenging to make new friends.”
- “After going through the physical changes I now have no self confidence and have lost all interest in meeting and getting to know people, feels like no one will ever be relatable and in the same place as me in life”

Low energy, fear of infections and frequent hospital visits were the top three factors contributing to negative impact of ALL

Respondents were asked what **factors** contributed to any negative impacts of ALL. 80 respondents answered this question. Responses are reflected in the chart below:

ANSWER CHOICES	RESPONSES	
Low Energy	85.00%	68
Fear of Infections	75.00%	60
Frequent Hospital Visits	71.25%	57
Depression/Anxiety	63.75%	51
ALL Symptom Burden	57.50%	46
Inadequate Nutrition	27.50%	22
Total Respondents: 80		

Some respondents elaborated on their answer:

- “I think about infections every minute of every day. I’m always thinking about when I can have my next nap. I want to get exercise to stay strong but I fear fainting on a walk because I have low blood pressure. I feel like a burden to my family and I wish I could contribute more and see improvements in my health as I go through treatment but I continuously experience new or recurring side effects.”
- “It’s an all encompassing experience when your son is fighting for his life, has a wife & small baby that all needed to live with us (his parents) while going thru this journey (they live in Abbotsford & he needed to be closer to VGH when not actually admitted to hospital) However we were very thankful we weren’t further than Surrey. We met some who were much further & had to find accommodation in the city.”
- “Isolating during treatment, especially because of COVID, losing hair, body was always swollen so I looked bigger than the number on the scale, hated my appearance, was not in a place mentally to talk to a therapist at the time and still feel struggle to discuss”

4. Experiences With Currently Available Treatments

CADTH examines the clinical benefit and cost-effectiveness of new drugs compared with currently available treatments. We can use this information to evaluate how well the drug under review might address gaps if current therapies fall short for patients and caregivers.

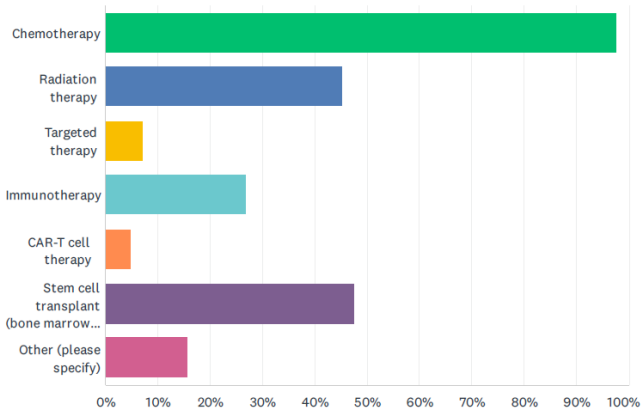
Describe how well patients and caregivers are managing their illnesses with currently available treatments (please specify treatments). Consider benefits seen, and side effects experienced and their management. Also consider any difficulties accessing treatment (cost, travel to clinic, time off work) and receiving treatment (swallowing pills, infusion lines)

Currently available treatments received for ALL

Respondents were asked which types of ALL treatment have you or your loved one received? Select all that apply. 82 respondents answered this question.
Chemotherapy – 80/82 (97.56%)
Stem cell transplant (bone marrow transplant) -- 39/82 (47.56%)
Radiation therapy – 37/82 (45.12%)
Immunotherapy – 22/82 (26.83%)
Targeted therapy – 6/82 (7.32%)
CAR-T cell therapy – 4/82 (4.88%)
Other - 13/82 (15.85%) Listed: natural medicine, Chinese medicine, sound baths, meditation, transfusions and other treatment medications such as steroids and anti-emetics

Q11 Which types of ALL treatment have you or your loved one received? Select all that apply.

Answered: 82 Skipped: 28



Fatigue and Neutropenia were the most severe side effects of current treatments (not blinatumomab)

Respondents who answered that they did not receive blinatumomab treatment for ALL were asked to rate the severity of the side effects they experienced from their ALL treatment(s) (from 1- did not experience to 4 – severe). Collective responses were measured by weighted average. 63 respondents answered this question.
Fatigue or weakness – 3.56/4
Neutropenia (low white blood cells) – 3.26/4
Thrombocytopenia (low platelets) – 2.97/4
Infections (bacterial, viral, fungal) – 2.87/4
Nausea or Vomiting – 2.87/4
Diarrhea – 2.82/4
Anemia (low red blood cells) – 2.73/4
Fever – 2.49/4
Peripheral Edema (swelling of arms, legs, or other body parts) – 2.42/4
Headaches – 2.41/4
Infusion Reactions (chills, rash, difficulty breathing) – 2.08/4
Neurological Symptoms (confusion, seizures, difficulty speaking) – 1.92/4
Cytokine Release Syndrome (CRS) – 1.15/4

These side effects had significant negative impact on life which included hospitalization, and lower functionality.

Some respondents elaborated on their treatment side effects:

- “I had many hospitalizations for infections, and one stint in the ICU due to seizures/stroke as a side effect of one of the chemo drugs. I lived in fairly consistent fear that I would be killed by an infection before I had a chance to survive.”

- “Pancreatitis multiple times severe leg cramps and pain neuropathy in feet and hands blurry vision joint pain abdominal pain thrombosis in heart ascites ulcerative colitis”
- “Loss of weight (50%), discoloration and darkening of skin colour, severe constipation during chemotherapy, loss of mobility in all limbs.”
- “Mucositis (of my mouth) made it painful and difficult to eat and sleep. Anxiety and panic attacks and heart palpitations - needing lorazepam when overwhelmed.”
- “My son had tumour lysis syndrome after his first treatment. He was at risk for a stroke and required multiple dialysis treatments in the ICU.”
- “Weight gain (severe- 65 pounds) Neuropathy (moderate) Intense muscle and joint pains (severe)”

5. Improved Outcomes

CADTH is interested in patients’ views on what outcomes we should consider when evaluating new therapies. What improvements would patients and caregivers like to see in a new treatment that is not achieved in currently available treatments? How might daily life and quality of life for patients, caregivers, and families be different if the new treatment provided those desired improvements? What trade-offs do patients, families, and caregivers consider when choosing therapy?

In new treatments patients expressed a desire to gain a longer remission but side effects were an important consideration. Quality of life during treatment is important to patients.

Respondents were asked, How would you feel about a new treatment that could offer a longer remission from ALL? Select all that apply. 53 respondents answered this question. Answers are reflected in the chart below:

ANSWER CHOICES	RESPONSES	
Very hopeful	62.26%	33
Anxious about potential side effects	24.53%	13
Anxious about the unknowns of the treatment	22.64%	12
Cautiously optimistic but uncertain	18.87%	10
Somewhat hopeful	16.98%	9
I don’t know	15.09%	8
Skeptical about its effectiveness	11.32%	6

Respondents were asked, How important is it to you to achieve longer remission, even if the new treatment might come with increased risks or uncertainties? 52 respondents answered this question:

28/52 (53.85%) – Very important
17/52 (32.69%) -- Somewhat important
7/52 (13.46%) – Not important

Respondents were asked to choose the top factors that are most important to them when considering new treatment options. 70 respondents answered this question. The top 4 answers were:

Quality of life during treatment – 51/70 (72.86%)
Number/Severity of side effects – 49/70 (70%)
Length of time in potential remission – 31/70 (44.29%)
Financial costs -- 31/70 (44.29%)

6. Experience with Drug Under Review

CADTH will carefully review the relevant scientific literature and clinical studies. We would like to hear from patients about their individual experiences with the new drug. This can help reviewers better understand how the drug under review meets the needs and preferences of patients, caregivers, and families.

How did patients have access to the drug under review (for example, clinical trials, private insurance)? Compared to any previous therapies patients have used, what were the benefits experienced? What were the disadvantages? How did the benefits and disadvantages impact the lives of patients, caregivers, and families? Consider side effects and if they were tolerated or how they were managed. Was the drug easier to use than previous therapies? If so, how? Are there subgroups of patients within this disease state for whom this drug is particularly helpful? In what ways? If applicable, please provide the sequencing of therapies that patients would have used prior to and after in relation to the new drug under review. Please also include a summary statement of the key values that are important to patients and caregivers with respect to the drug under review.

Access to/coverage of blinatumomab

18/82 (21.95%) respondents stated that they or the person they care(d) for were treated with blinatumomab for ALL. Of these 18 respondents, 15 answered the question, How did you get access to blinatumomab?

Clinical trial – 5/15 (33.33%)
Compassionate use program (through pharmaceutical company) – 4/15 (26.67%)
Paid for by private insurance -- 1/15 (6.67%)
Paid for out-of pocket – 0/15
5/15 (33.33%) answered “other” - 2 respondents stated that they did not know. 1 stated: RAMQ - Quebec socialized healthcare. 1 said government funding.

Blinatumomab was efficacious in treating ALL

Respondents were asked, Did your ALL respond to blinatumomab? 15 respondents answered this question:

10/15 (66.67) answered – Yes, completely
3/15 (20%) answered – Yes, partially
2/15 (13.33%) answered – No, it did not

Side effects of blinatumomab

None of the respondents with experience in blinatumomab indicated that the side effects were severe. This indicates a tolerable treatment.

Respondents were asked - If applicable, rate the severity of the side effects of blinatumomab treatment that you experienced (from 1- did not experience to 4 – severe). Collective responses were measured by weighted average. 15 respondents answered this question:

Neutropenia (low white blood cells) – 2.29/4
Fatigue or weakness – 2.27/4
Fever – 2/4
Anemia (low red blood cells) – 1.71/4
Thrombocytopenia (low platelets) – 1.71/4
Infections (bacterial, viral, fungal) – 1.64/4
Headaches – 1.57/4
Neurological Symptoms (confusion, seizures, difficulty speaking) – 1.53/4
Cytokine Release Syndrome (CRS) – 1.5/4
Diarrhea – 1.47/4
Peripheral Edema (swelling of arms, legs, or other body parts) – 1.47/4
Nausea or Vomiting – 1.4/4
Infusion Reactions (chills, rash, difficulty breathing) – 1.27/4

Some respondents elaborated on their treatment experience with blinatumomab:

- “I underwent neurological tests every few days. Initially at the beginning of the two rounds, I was hospitalized to closely monitor my reactions. Typically, the first 48 hours were the most challenging (fever, uncontrolled shakes), but then my body seemed to adapt. The medication was administered via a portable pump, which allowed me to be an outpatient after the initial reaction. The blinatumomab treatment led to my remission, enabling me to move forward with the stem cell transplant. Blinatumomab was a significant turning point in my treatment. I am eager to share my experience and advocate for others, as I was unaware that this treatment is not accessible to all Canadians. This needs to change.”

- “I had a low-grade fever for a couple of days following the start of my first round of blinatumomab, but it resolved quickly and was not linked to any infections.”

- “I tolerated Blina very well but was told that my cancer would likely come back and was recommended to get a stem cell transplant but 8 months after that transplant it came back. That is when car t came in.”

- “Lots of fevers and increased heart rate, high blood pressure.”

Approxiately 53% of patients reported that blintumomab indicated that the treatment was less difficult than others they had taken.

Respondents were asked, Overall, how does blinatumomab compare to other treatments you have had for ALL? 15 respondents answered this question.

6/15 (40%) -- Same
4/15 (26.67%) – Much less difficult
4/15 (26.67%) – Less difficult
1/15 (6.67%) – More difficult

Some respondents elaborated on their experience with blinatumomab compared to other treatments for ALL:

- “After experiencing initial neurological side effects, I found the treatment to be less daunting than the side effects of chemotherapy and radiation. As an outpatient, I was able to focus on staying active, ensuring proper nutrition, isolating safely at home, and spending quality time with my husband, all as part of the preparation strengthening myself for the stem cell transplant. I am a staunch advocate for immunotherapy and play an active role in supporting research in this field.”

- “I helped my local hospital pilot a program where patients can take home a pump and be continuously infused at home. While I got to take my treatment home, it still came with some challenges, including bathing and getting around with my portable bag while avoiding snagging the tubes on anything.”

- “I am grateful to get this treatment because the side effects were very mild overall. And I know positive effects of this medicine.”

- “Less severe nausea than chemo, same amount of neutropenia, more hospitalizations than chemo due to CRS”

60% of patients felt that quality of life on blinatumomab was better compared to other treatments. Receiving the treatment at home was a valued benefit.

Respondents were asked to rate how much they agree or disagree with the statement: "blinatumomab improved my quality of life compared to other treatments I have received." 15 respondents answered this question.

6/15 (40%) – Strongly agree
5/15 (33.33%) – Neutral
3/15 (20%) – Agree
1/15 (6.67%) – Disagree

Some respondents elaborated on the quality-of-life impacts of blinatumomab treatment:

- “It afforded me a quality of life unlike the months spent confined in a hospital; isolated & traumatized, with restricted physical activity, no social interaction, subpar food, and limited comfort from my husband.”

- “Just being able to receive the treatment while at home is a tremendous benefit, especially to mental health and somewhat to physical health (it’s easier to eat what you like at home than to be stuck with hospital mush).”

- “I could just live my normal life at home and getting the treatment at the same time. I was a virtual patient going to the hospital every day for 28 days per cycle to get my bag changed. Otherwise, I was very happy to get this treatment.”

- “The only issue was the 24-hour continuous infusion of the drug for 28 days, which impacted the quality of life. However, the side effects of the drug were very low compared to the chemotherapy treatment.”

- “Just prior to receiving Blina I had done the Dana-Farber protocol which was pretty intense so I believe if I were to have to choose between the two I would definitely go with Blina as I had less side effects.”

- “Although I didn't feel as sick from the treatment, I had to be hospitalized for basically the entire time I was receiving the blincyto because I would spike a fever and need to be treated for CRS”

- “I felt alive again and able to manage. Staying in the hospital for months at a time were slowly killing me, I was losing my drive for life. Blinatumomab and the freedom rekindled my spark for life. Please note...nature and being in nature is my blood of life and I went months being unable to be outside or off my hospital floor.”

- “The patient felt self conscious going out with his fanny pack and tubes visible. He was more comfortable in weather where we could wear a jacket to cover it.”

Most patients indicated that they were Likely to take blinatumomab again/recommend to other patients.

Respondents were asked “based on your experience with blinatumomab, would you take this again if your doctor recommended it for you?” 14 respondents answered this question:

11/14 (78.57%) – Yes
3/14 (21.43%) – No

Respondents commented:

- “It is far better to be at home than in the hospital, especially for my mental health.”

- “Effectiveness of this medicine. Can enjoy my daily life as I don't need to admit to the hospital to get the treatment.”

- “I would like to hope I never have to but I tolerated it better then chemo.”

- “Because it put me into remission”

Respondents were asked, Based on your experience with blinatumomab, would you recommend it to others with ALL? 16 respondents answered this question.

14/16 (87.5%) answered - Yes
2/16 (12.5%) answered - No

Some elaborated:

- “Chemo and radiation have lasting side effects that I feel blinatumomab did not.”
- “Low risk of side effects with a high probability of putting a patient in complete remission, ability to do treatments at home and maintain some level of independence.”
- “Only if the other option is chemotherapy. However, my treatment was supplemented eventually with a stem cell transplant as my oncologist recommended that it's still not a long term solution for Leukemia treatment.”

Key values of patients and caregivers regarding new treatment options for ALL

Respondents were asked to choose the top factors that are most important to them when considering new treatment options. 70 respondents answered this question. The top 4 answers were:

1. Quality of life during treatment – 51/70 (72.86%)
2. Number/Severity of side effects – 49/70 (70%)
3. Length of time in potential remission – 31/70 (44.29%)
4. Financial costs -- 31/70 (44.29%)

7. Companion Diagnostic Test

If the drug in review has a companion diagnostic, please comment. Companion diagnostics are laboratory tests that provide information essential for the safe and effective use of particular therapeutic drugs. They work by detecting specific biomarkers that predict more favourable responses to certain drugs. In practice, companion diagnostics can identify patients who are likely to benefit or experience harms from particular therapies, or monitor clinical responses to optimally guide treatment adjustments.

What are patient and caregiver experiences with the biomarker testing (companion diagnostic) associated with regarding the drug under review?

Consider:

- Access to testing: for example, proximity to testing facility, availability of appointment.
- Testing: for example, how was the test done? Did testing delay the treatment from beginning? Were there any adverse effects associated with testing?
- Cost of testing: Who paid for testing? If the cost was out of pocket, what was the impact of having to pay? Were there travel costs involved?
- How patients and caregivers feel about testing: for example, understanding why the test happened, coping with anxiety while waiting for the test result, uncertainty about making a decision given the test result.

<Enter Response Here>

8. Anything Else?

Blinatumomab, presents as a promising treatment option, particularly for its balance between effectiveness and manageable side effects. Respondents find the predictable side effects and the potential for prolonged remission significantly meaningful. The continuous infusion aspect, while initially appearing cumbersome, actually provides a unique advantage by allowing patients to maintain a semblance of normalcy and independence. This quality of life enhancement is invaluable, as it not only supports the patients but also alleviates the burden on their families, promoting greater health equity.

Appendix: Patient Group Conflict of Interest Declaration

To maintain the objectivity and credibility of the CADTH reimbursement review process, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This Patient Group Conflict of Interest Declaration is required for participation. Declarations made do not negate or preclude the use of the patient group input. CADTH may contact your group with further questions, as needed.

1. Did you receive help from outside your patient group to complete this submission? If yes, please detail the help and who provided it.

   No

2. Did you receive help from outside your patient group to collect or analyze data used in this submission? If yes, please detail the help and who provided it.

   No

3. List any companies or organizations that have provided your group with financial payment over the past 2 years AND who may have direct or indirect interest in the drug under review.

Table 1: Financial Disclosures

Check Appropriate Dollar Range With an X. Add additional rows if necessary.

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Amgen Inc.				X

I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

Name: Christina Sit
Position:Manager Community and Strategic Partnerships
Patient Group: The Leukemia & Lymphoma Society of Canada
Date:November 25

CADTH

CADTH Reimbursement Reviews
Patient Input Template

Name of Drug: 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.
Name of Patient Group: The Leukemia & Lymphoma Society of Canada (LLSC), Ac2orn, and OPACC
Author of Submission:

1. About Your Patient Group

The Leukemia & Lymphoma Society of Canada (LLSC) - bloodcancers.ca

LLSC is a national charitable status organization dedicated to finding a cure for blood cancers and its ability to improve the quality of life of people affected by blood cancers and their families by funding life-enhancing research and providing educational resources, services, and support. The Leukemia and Lymphoma Society of Canada (LLSC) is the largest charitable organization in Canada dedicated to blood cancer. Our focus includes:

- Funding blood cancer research from bench to bedside.
- Rethinking how a person navigates their blood cancer experience
- Providing targeted blood cancer information
- Offering tools for psychological and emotional support
- Empowering Canadians to take charge of their blood cancer experience through practical support and advocacy

Advocacy for Canadian Childhood Oncology Research Network (Ac2orn) - http://www.ac2orn.com

Ac2orn is committed to advocating for translational research and effective treatments to realize the goal of curing childhood, adolescent, and young adult cancers. Ac2orn is a national organization made up of childhood, adolescent, and young adult cancer advocates and survivors, across all cancer types, and in different stages of the cancer experience.

Ontario Parents Advocating for Children with Cancer (OPACC) - http://www.opacc.org/

OPACC will be the leading voice and expert resource for families and organizations navigating the childhood cancer journey.

Childhood Cancer Canada https://www.childhoodcancer.ca

The mission of Childhood Cancer Canada is to uplift children diagnosed with cancer and their families by increasing financial support, setting survivors up for academic success, and inspiring hope for improved treatment and survival outcomes.

2. Information Gathering

In November 2024 LLSC conducted three one-on-one interviews with three caregivers of pediatric patients with B-Cell Acute Lymphoblastic Leukemia (ALL) who received blinatumomab treatment.

Two of the children treated were aged 2 at the time of diagnosis, and one child was 10 years old at diagnosis. Two are residents of Ontario and one resides in British Columbia.

As this treatment has previously been reviewed in pediatric ALL, input from this population of patients and/or caregivers regarding disease experience and experience with currently available treatments has previously been gathered and submitted to the CDA (formerly CADTH) for consideration.

To avoid repetitive questioning and to minimize emotional strain and undue harm on participants, we concentrated our recent interviews on specific areas. We focused on:

- patients' and caregivers' experiences with administering blinatumomab treatment at home and
- comparing quality of life during blinatumomab treatment with their experiences with prior treatments for pediatric ALL.

Please consider our previously gathered and submitted input regarding an earlier review of this treatment for this patient population. Previous review found here - https://www.cadth.ca/blinatumomab-blincyto-acute-lymphoblastic-leukemia-pediatric-details

Please also consider our most recent previously submitted input regarding this pediatric treatment, which was submitted to the CDA for consideration in August 2024 but has not yet been made publicly available.

3. Experiences with Currently Available Treatments

The current standard of care for Canadian pediatric patients with B-cell ALL are chemotherapy infusions developed more than 50 years ago, often accompanied by serious side effects for the patient and only able to be administered in hospital.

All the caregivers we interviewed talked about the negative impact of chemotherapy on their patients' physical health, with serious side effects from infusion.

One caregiver, whose patient was 10 years old when she was diagnosed with B-cell ALL, shared her daughter's experience with currently available treatment for the disease:

"After diagnosis, they started treatment right away. There was a month of induction chemo and high dose steroids and then another bone marrow aspirate at the end of that to see where they've gotten to and she was not in remission at that point. So [healthcare team] wanted to carry on with consolidation chemo… she just absolutely felt like shit the whole time, like listless, and we just let her be on a device basically the whole time, because that's all she could do to get through the days. Then they did another bone marrow aspirate and it was still not at 0. And then the plan was then to go to two rounds of blina which are 28 days each round… in preparation for bone marrow transplant."

Another caregiver talked about the experience when her 2-year-old daughter was getting infusion (chemotherapy), and again when she relapsed at age 6 and went back on chemotherapy:

"They had to give her an infusion for, an hour, 2 hours to make her pee, to make sure her pee was the right consistency so they could give her the chemo to make sure the chemo was coming out so it didn't destroy her bladder. Like it's a lot… She looked like she was dying… the Vincristine she was getting that didn't work the first time around, it was made in what, the 50s or 60s.""

A third caregiver's son, 2 years old at time of diagnosis, was put on a high-risk protocol of chemotherapy (he had leukemia cells in his spinal fluid). Then serious health complications meant he had to come off chemotherapy and couldn't return to chemotherapy infusion:

"He caught a virus during chemo; his immune system was weakened. He was very sick, an inpatient for 7 weeks, his viral load was in the millions. He had to stop chemo while they treated the virus. Then the doctors didn't want to go back to the intense chemo he was on, so he was switched to blinatumomab. They thought blinatumomab doesn't knock out an immune system out as badly, and targets leukemia cells… they reassured me that blinatumomab, as a newer approach, was possibly even better than infusion, and gave us more mobility freedom."

Long hospitalization stays required for traditional chemotherapy infusion also had negative impacts on the emotional health of the caregiver and other family members such as siblings.

"I did need a lot of emotional support during infusion treatment – I was vocal about it and reached out and got support from social workers at the hospital…We take mental health very seriously in our family. Our oldest son was seeing a therapist regularly. He was the odd one out [during brother's hospitalization period]."

4. Experiences with Drug Under Review

The three caregivers interviewed said they and their patients had overall positive experiences with blinatumomab, especially in comparison to infusion. Due to outpatient treatment and 'gentler' effects of blinatumomab, the patients were able to live with family, play with peers, and stay out of the hospital.

Starting blinatumomab and side effects

One caregiver, recommended blinatumomab when her daughter relapsed, said she was nervous at first about the new treatment and sought a second medical opinion:

"I didn't understand what 'gentle' would mean. I was very upset that she relapsed. I wanted to hear more about blinatumomab. So my doctor set me up with a doctor in Toronto and she explained it really nicely saying how, like the T cell will attach to the B cell and it's like a little rod in between and then, it kind of transfers the information to kill the leukemia itself... I thought OK if this is something new, they're putting in protocol and they're saying it's gentler and it's not destroying every cell in her body, it's actually targeting the bad ones, leaving the good ones alone. I was all for it... "We saw the relative gentleness of the blinatumomab compared to the infusion."

A caregiver noted she was nervous about starting blinatumomab on her then 3 year-old boy, who had high-risk B-cell ALL and had to stop chemotherapy treatment due to a serious virus.

"With blinatumomab, the first couple days in hospital he had substantial fevers, some pain, and was not tolerating blinatumomab at all at first. I was sceptical and scared those first few days... I had a friend whose son had been through blina and assured me that the first days were rough and got better which it did."

Another caregiver whose daughter, relapsed at age 6, experienced a fever upon starting blinatumomab, said that she had been forewarned by healthcare professionals that it could happen and was monitored in hospital.

"Her fever just went woah! Like, right up. But they did tell me before this that could start with blinatumomab and they compared it to like a flu shot. You might get a fever. Your body's like fighting all

this. Didn't last long. But that's why they want you there [in hospital at the start], *right?*

The caregiver of the older patient (age 10/11) said she experienced no side effects from blinatumomab.

"No fever. Like nothing. No side effects at all… every 4 days we went in for a [blinatumomab] bag change and they would have her do a signature or write her name and ask her a couple of questions [for cognitive testing*]. There was nothing untoward with that. Never."*

For all the patients, cognitive testing was done routinely, at every bag change for blinatumomab, to check for neurological damage as a side effect. None was discovered in any of the patients, their caregivers told us.

The mother of a child diagnosed at age 2, and 6 years old when she relapsed, said that cognitive testing was conducted through blinatumomab treatment, with no adverse side effects detected:
"We got to have her write her name to make sure neurologically, nothing's going wrong with her, that she can still hold a pencil so she can write without shaking all over the page and we'll monitor that and she'll have more nursing for the first three days."

For the caregiver whose child was a toddler while getting blinatumomab, "*cognitive testing was minimal because he was then preverbal and unable to write or read yet."* Now aged 5 and in remission, *"he's doing well in all-day kindergarten"* she said.

Delivery system of blinatumomab

Blinatumomab requires a new bag of medication every 4 days that can only be done by the cancer clinic/hospital treating that patient. As well as those visits, for some a long drive, the same distance of drive was required for any glitches in the blinatumomab delivery system that need adjusting.

One caregiver talked about initial training for the blinatumomab, given at the cancer centre where her daughter was treated, and some of the forecasting on potential issues such as the blinatumomab pack system 'beeping' when something needed adjusting.

"Before we went home, they told us what to do, how to do it [administer blina]. *We were anxious to get home and we just knew if something goes wrong, we're heading on back* [to the cancer centre]. *They're like, OK, if something happens with it, if it beeps, you have to come back."*

Another caregiver, herself a nurse, said that she wouldn't feel comfortable changing the blinatumomab supply by herself. She and her patient had to drive a total of 5 hours each time for a bag change. With changes required every 4 days over a 28-day period, that added up to 35 hours of driving – not including the times they had to take in the blina system for troubleshooting glitches.

"London is about a 2 1/2 hour drive from our house each way. If there was a beep on that machine, Windsor [their nearest hospital] *was not allowed to touch that bag. We had to drive to London Children's Hospital… we'd be getting an 'air-in-line code' on your pump, like champagne bubbles. The nurses* [in London] *would clear it, they flipped the line to get the bubbles through, and that was our biggest problem with it.*

That was one thing I would like to see. That more hospitals be taught how to do blina, like for air-in-lines and codes like that, it would be a big help if you could go to a local hospital for it."

One caregiver said that even at the treating hospital where they received the blinatumomab and had it replaced, she experienced shortcomings in the knowledge of healthcare professionals about blinatumomab's delivery method.

"Because it's a newer therapy, the nurses were not confident with it, they were apprehensive about it, checking lists, I could feel that as a caregiver. We would sometimes get confusing, mixed information from different nurses. For example, normally you hang a medication bag to get air out. But blinatumomab is not like that; sometimes I felt I had to explain it to the nurses as to how it gets placed in the backpack."

Some of the caregivers said they experienced unsuitability and limited options from the healthcare system for the (backpack) delivery system for blinatumomab. They figured out their own solutions.

In cases of very young patients, some parents preferred the traditional IV pole as the backpack was too heavy for their little ones. The submitters of this document recommend that a variety of backpacks and carriers be offered so that solutions can be tailored.

The caregiver of the toddler boy had to adjust and buy her own backpack to suit his child's activity level and size:

"We were sent home with a one-shoulder sling bag, not ideal for a 2-year-old. I gave that feedback to the oncology team and they said 'it's all we have.' I ended up buying a kid-sized hydration backpack instead. It wasn't too heavy for him, he could still play. It just became a part of him. My boys are very active, very physical – and it did not hold him back at all… just a few times he didn't want to get his backpack on, he'd jump up and go out of bed. At sleep time, we used a hook on the wall above his headboard. The tubing is quite long and he rolls around in bed, occasionally he would get a bit wrapped up in tubing, but he never got so tangled that it came out."

The caregiver whose daughter was given blinatumomab at age 6 said her patient opted out of wearing the backpack and came up with their own solutions:

"The backpack was a bit heavy, there's a weight to it. You think, oh, it's just a little bit of medicine. I was surprised when I picked it up. I remember one time she put it on and she was like, whoa, and she, like, fell backwards in it. She was like, I don't want this on me…we have a community group around here for pediatric oncology and they have specialized IV poles they donate… the IV pole was great. We just hung up the medication there, which was better because the bag isn't rustling around on her now, it is more of a secure structure. She just walked around with her IV pole, just like in the hospital – but she was at home, so she didn't mind."

*"At bedtime we pushed the IV pole right up to her bed, because you can't just lay it [blinatumomab] down because when you think of liquid, if it lays flat, it's not going to get through and if it doesn't get through the tube, that machine's going to beep… you don't want to hear that beep so with it hanging on the IV pole it was a big help at bedtime. I probably overdid it, I stuffed pillows around her so she wouldn't roll. Like, just lie on your back, don't move. But that was a big deal with keeping it from beeping… the first night we got home, it went beep beep beep… I think we got home [*from their treating hospital] *at 4 am. The nurses were like, we are so sorry, they literally took it out, flicked the line, flipped it back and cleared it… the second night it did the same thing again. The nurses were like, we have to think of something better. So they walked us through how to clear it on the machine. After that probably 3 times a day we would flick the line and the beeping stopped most of the time.*

Another caregiver, whose daughter was given blinatumomab, said it was an easy transition to the backpack, both for the patient's use, and in terms of the treating hospital being close to their home.

"They provided her with a little backpack and they had to cut a little hole in the top to put kind of like a zip tie to hold the bag up and it was just the bag and the pump in there. And then I always put an extra like central venous line emergency kit in there... It didn't really bother her. She got used to it, even in the middle of the night, to go to the bathroom she would remember to grab it and we never really had any issues with it pulling. She was quite cautious, but again, she's at that time 11... she was fine with it and remembered about it, was mindful of it."

*"We never had any error messages or beeps on the [blina] pump... between the pump and the patient, there's a filter and she [*the patient*] noticed it was leaking. We called [*the hospital*] and they said you better come in. They got the whole line changed out; that happened twice but nothing beeped, ever. It was strange."*

Quality of life

All 3 caregivers related that blinatumomab made a big difference to the quality of life for their patients, and themselves and the rest of their families, compared to traditional chemotherapy infusion.

The caregiver of the 10 year old patient kept a written record every day during blinatumomab treatment; she got out the record book during our interview with her:

"Two weeks after she started blinatumomab, she was going for walks, going outside with friends... I don't think she ever missed a horse therapy no matter what she felt like. So she was doing that and then back to doing some artwork, and she would want to go out. Usually in the evening she would feel a little more energetic and she'd go outside and there'd be neighbourhood kids playing, and maybe she wouldn't be playing, but she'd sit and watch them and maybe get up and scooter for a minute or something like that...

In comparison with induction and consolidation it was like night and day. Her appetite came back, she had energy. Despite being hooked up 24/7 with her little backpack, she was walking to the corner store, riding her bike, wanting to play, wanting to engage with her brother, so everything social wise that would be normal for a kid she was interested in again... So huge, huge positive change. She still was bothered by the fact that she had to go every week to have port needle changes, have the dressing change, but it

was really nothing compared to having to go in knowing that she had to have chemo and blood transfusions and all of that."

One caregiver said her child, who was immobilized in bed or wheelchair for 3 months in hospital, was able to walk and even dance around the home within a week or two of being on blinatumomab:

"They [doctors] did say it would be more gentle than the chemo, which I didn't really believe at the time. Then she started it - and it was so much nicer, it was such a better experience then traditional chemotherapy. She wasn't sick. She wasn't throwing up. She got home and within a week, maybe two of being on the blina, and the chemo kind of clearing from her, she was moving! She had her little blina in her arm, which I thought was the best spot. It was really nice for her there and she would just hold on to her tube and she was up and she was dancing…It's the oncology kids' normal even when they're hooked up in the hospital. They get used to it real fast."

"*As COVID was going on, so she was in virtual learning and she would sit on her computer and listen to her teacher with her IV pole in the background. She was doing her schooling through the whole thing. She was fine."*

The caregiver of a 2 year old boy noted that take-home blinatumomab made a big difference in his quality of life compared to when he was being treated in-hospital with chemotherapy.

"He is very active, very physical – and it did not hold him back at all. The blinatumomab piece gave us so much more freedom. He could go home, he was playing on the monkey bars."

One caregiver said that her experience in support circles she belongs to (for caregivers of pediatric patients) reflect others' positive experiences with blinatumomab.

"I belong to two different Facebook groups of and, and every single thing I've seen, because other people post on there like, Oh my God, my kid is going on blina, what was your experience? And you read the comments and every single comment is like it was such a break. In that time, we felt like we had our kid back. It's everything to the kid, it's everything to the family to because you feel like you've completely lost your child and then they're able to feel a little bit more normal again."

Financial distress

One caregiver, when told the cost of blinatumomab, said she was prepared to sell the family home to pay for it. It turned that they did not have to pay for it, but the extreme distress about how to absorb the cost for vital treatment of their child was real:

*"Our pharmacist came up to me in the hospital and said you have to send this letter to your insurance company… we were denied. I'm like but it's in her treatment plan and it's supposed to start in a week or so… I haven't slept in 3 months, I'm holding my wallet and saying to him [*pharmacist*] 'please don't take blinatumomab away from her. I spoke with Toronto [*doctors*] and they said this is the future of medication. She has to have it. I will pay for it, how much is it, I have my credit cards… he said it starts around $100,000. I breathed out and my legs went all funny and I just looked at him and said 'I'm going to sell my house tomorrow…I was totally ready to go live in my van if we have to… he was very nice, he could see I was having a nervous breakdown. He's like, don't put your house up for sale, there are other ways, we'll figure it out… honest to goodness I thought I was going to get a bill in the mail, I still in the back of my mind do."*

One caregiver shared that she was shocked that blinatumomab is not widely available or funded.

"So, you're completely good with giving her this medication from 1956 that's going to destroy everything, but something new, you're worried you're worried about it? Something new with data behind it? I don't wanna be rude… but I don't understand. If you have this medication sitting on the shelf and ALL is the number one [blood cancer] for kids, do it. Do something!"

5. Improved Outcomes

Some suggestions for the healthcare system coming out of these caregiver interviews are as follows:

A) Provide caregivers tips and tools on what to expect with the blinatumomab delivery system, some at-home solutions (how-to guide/instructions) to help to alleviate practical challenges (driving to cancer centre at unexpected times of day/night).

B) Train more nurses at local hospitals in the administration/delivery method of blinatumomab would save caregivers and patients the burden of having to driving long distances to their cancer centre as the sole place to replace bags and tweak the delivery system. Also extend knowledge and skills at the cancer centres where blinatumomab is handled.

C) Provide more choices in the delivery system backpacks for patients using blinatumomab; include a few choices based on body size and fitness/strength of the patient.

7. Companion Diagnostic Test

8. Anything Else?

Is there anything else specifically related to this drug review that CADTH reviewers or the expert committee should know?

<Enter Response Here>

Appendix: Patient Group Conflict of Interest Declaration

To maintain the objectivity and credibility of the CADTH reimbursement review process, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This Patient Group Conflict of Interest Declaration is required for participation. Declarations made do not negate or preclude the use of the patient group input. CADTH may contact your group with further questions, as needed.

1. Did you receive help from outside your patient group to complete this submission? If yes, please detail the help and who provided it.

   No

2. Did you receive help from outside your patient group to collect or analyze data used in this submission? If yes, please detail the help and who provided it.

   No

3. List any companies or organizations that have provided your group with financial payment over the past 2 years AND who may have direct or indirect interest in the drug under review.

Table 1: Financial Disclosures

Check Appropriate Dollar Range With an X. Add additional rows if necessary.

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Amgen Inc.				X

I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

Name:
Position:
Patient Group: The Leukemia & Lymphoma Society of Canada (LLSC)
Date:

CADTH

CADTH Reimbursement Review

Clinician Group Input

CADTH Project Number: PC0365-000
Generic Drug Name (Brand Name): Blinatumomab
Indication: Acute Lymphoblastic Leukemia
Name of Clinician Group: Canadian Leukemia Study Group (CLSG)/Groupe Canadien d'Étude Sur La Leucemie (GCEL)
Author of Submission: Andre Schuh

1. About Your Clinician Group

CLSG/GCEL is a cross-Canada collective of acute leukemia treating physician representing all major leukemia centres in all provinces. The CLSG incorporation documents of 23.10.2019 define the purpose of CLSG/GCEL:

'To improve the diagnosis and treatment of leukemia in Canada, by identifying diagnostic and management best practices, promoting Canada-wide standards-of-care, fostering clinical and basic leukemia research, and improving new drug access.'

The CLSG/GCEL website: https://www.clsg.ca/

2. Information Gathering

CLSG board members are all leukemia physicians working in an academic, university-based treatment setting. CLSG opinions are evidence- and literature-based, and are buttressed by extensive collective experience. CLSG opinions and positions are defined via ongoing group discussions and polling of members, with input requested from other international experts, as appropriate. Written opinions are reviewed, edited, and approved by the group.

3. Current Treatments and Treatment Goals

The goal of treatment of Adult B-cell Acute Lymphoblastic Leukemia (B-ALL) is curative in intent.

Patients are initially treated with highly toxic, multi-agent, intensive chemotherapy protocols with the goal of achieving a complete remission (CR). The patients will then proceed to further post-remission treatment consisting of consolidation (also called 'intensification') chemotherapy, followed by maintenance chemotherapy. Depending on the exact protocol used (this is institution- and patient age-specific), in addition to systemic chemotherapy, patients will also receive intrathecal chemotherapy (up to 14 times, depending on the protocol used), to treat possible CNS leukemia. The entire B-ALL treatment may take more than two years to complete, and is extremely toxic.

Some patients (for example, those that require more than one induction cycle to achieve CR, those with high-risk genetic abnormalities such as *KMT2A* abnormalities, or patients with detectable measurable residual disease (MRD; see below), among others) may proceed to allogeneic hematopoietic stem cell transplantation (alloSCT) in first CR. However, most adult patients with B-ALL in first CR no longer require alloSCT.

With the approach outlined above, the vast majority of patients with B-ALL will achieve a first CR, and with a 3-year survival of >70%. However, a proportion of patients (<50%) will experience disease relapse, and will require retreatment.

The drug in question, blinatumomab (Blincyto), currently is approved in Canada for two B-ALL indications, one before first relapse, and one after first relapse.

1. First, blinatumomab is approved for patients achieving CR, but with measurable residual disease (MRD) at a level of ≥ 10-3 (0.1%) after at least 2 cycles of intensive chemotherapy (this is at ~12 -14 weeks after the start of treatment in our hands). Residual MRD at this treatment time-point is known to be associated with inferior outcomes. Current dogma suggests that such MRD+ve patients should also proceed to alloSCT. But notably, for patients proceeding to alloSCT, outcomes for patients MRD -ve at the time of transplant are superior to those of patients transplanted when MRD-ve.

Blinatumomab given for the 'MRD indication' is highly effective in eliminating MRD at 12-16 weeks in patients whose ALL cells express CD19 (>95%). However, even with the elimination of MRD at this timepoint, such patients should ideally still proceed thereafter to alloSCT, if at all possible.

2. Second, blinatumomab is also indicated for relapsed or refractory (R/R) CD19 +ve B-ALL. The goal of treatment for R/R ALL is to achieve another CR (CR 2 or higher) and then to proceed to alloSCT, if at all possible. Notably, in the R/R setting, CR rates with blinatumomab are >2 times higher than are CR rates after conventional intensive salvage chemotherapy. Other approaches in specific R/R B-ALL settings (but beyond the scope of this discussion) include Inotuzumab or CAR T-cell therapy. In our hands, blinatumomab is used most commonly for R/R B-ALL.

In both indication 1. and 2., blinatumomab leads to statistically significant improvement in overall survival, compared to conventional chemotherapy approaches.

The considerable efficacy of blinatumomab in both the R/R MRD+ve settings, suggests that earlier use of blinatumomab (i.e. prior to treatment failure as defined by disease relapse or post chemotherapy MRD positivity) may lead to further improvements in disease outcomes. Earlier use of blinatumomab, taken together with its efficacy) may also permit the development of treatment strategies that employ less conventional chemotherapy and corticosteroids. The latter two lead to the extreme toxicity of conventional ALL treatment. Earlier blinatumomab use may thus improve outcomes, while also reducing toxicity.

4. Treatment Gaps (unmet needs)

4.1. Considering the treatment goals in Section 3, please describe goals (needs) that are not being met by currently available treatments.

As outlined in Section 3 above, current treatment is given with curative intent. But while there have been improvements in adult B-ALL outcomes over the last 15 years, overall outcomes remain inferior with much room for improvement. In particular, CR rates could be higher, relapse rates could be lower, and median overall survival could be longer. Also, conventional treatment of ALL with multiagent chemotherapy and corticosteroids is extraordinarily toxic.

So, goals going forward would be to improve outcomes, while also reducing toxicity.

The considerable efficacy of blinatumomab in both the R/R MRD+ve settings, suggests that earlier use of blinatumomab (i.e. prior to treatment failure as defined by disease relapse or post chemotherapy MRD positivity) may lead to further improvements in disease outcomes. Earlier use of blinatumomab (taken together with its efficacy) may also permit the development of treatment strategies that employ less conventional chemotherapy and corticosteroids. The latter two lead to the extreme toxicity of conventional ALL treatment. Earlier blinatumomab use may thus improve outcomes, while also reducing toxicity. In addition, earlier use of blinatumomab may also reduce the need for alloSCT. The latter would not only be 'toxicity sparing' for patients (alloSCT is extremely toxic) might also be expected to also result in cost-savings for the system.

The current discussion is regarding the use of blinatumomab during consolidation. This is an earlier timepoint in B-ALL treatment than when blinatumomab is currently available. Moreover, the E1910 study upon which the current application is based, not only demonstrated that blinatumomab given at an earlier timepoint (consolidation), not only improves relapse-free and overall survivals, but that this dramatic effect is observed in both MRD+ve and MRD-ve cases. By extension, one can conclude that all B-ALL patients should be treated with blinatumomab. Longer remissions and fewer relapses (and thus possibly reduced use of alloSCT) should

result. The earlier incorporation of blinatumomab will also allow the true chemo- and corticocosteroid-sparing potential of blinatumomab to be realized, reducing toxicity, while shortening overall treatment duration.

There is currently no drug or other approach during consolidation (intensification) that can improve outcomes in this manner.

5. Place in Therapy

5.1. How would the drug under review fit into the current treatment paradigm?

Blinatumomab should be added to B-ALL treatment at an earlier timepoint in treatment (i.e. prior to treatment failure as defined by disease relapse or post intensive chemotherapy MRD positivity). Given during consolidation, Blinatumomab would be complementary to standard treatment, and might actually be chemotherapy- and corticosteroid-sparing. Overall, this approach would be less toxic, and possibly shorter.

The drug under review is disease eradicating rather than being symptom controlling in intent. That being said, the potential chemotherapy- and corticosteroid-sparing, and treatment-duration-shortening effect of earlier blinatumomab would also improve symptomatology by reducing toxicity.

For the proposed indication, blinatumomab would be used at an earlier timepoint in combination with conventional chemotherapy, and NOT as a later (or last) line of treatment.

For the proposed indication, blinatumomab would NOT be reserved for patients who are intolerant to other treatments or in whom other treatments are contraindicated. Rather, blinatumomab would be given to all patients, regardless of MRD status.

The results of the E1910 study are revolutionary in B-ALL treatment. The earlier use of blinatumomab (and independent of MRD status) defines a true change in standard of care (SOC). In our view, this will be the most important change in the up-front treatment SOC of adult ALL that we have witnessed in the last > 20 years.

It would not be appropriate to recommend that patients try other treatments before initiating treatment with the drug under review. The overwhelming message of the E1910 study is that blinatumomab should be introduced early, regardless of MRD status, and prior to treatment failure.

5.2. Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

According to the E1910 study, all adult patients with B-ALL in CR should receive blinatumomab in consolidation, regardless of MRD status. Of course, the leukemia cells of patients receiving blinatumomab should express the blinatumomab target, CD19. This would be almost 100% of cases (all new cases of B-ALL are tested routinely for CD19 expression). Also, to receive blinatumomab in consolidation, the patients would have to have achieved a CR with induction chemotherapy. This would be >80-90% of patients. Notably, patients not achieving a CR would be eligible for blinatumomab via the prior approval for R/R disease. The E1910 study did observe some effects of patient age on blinatumomab responsiveness, but even in the ≥ 55 years age group, blinatumomab was markedly better than chemotherapy alone with respect to overall survival. Also, age effects have not been observed in other studies of blinatumomab given during induction.

Patients for treatment would have to be CD19 +ve and also in complete remission. Both of these assessments are absolutely routine in ALL-treating centers. There are no issues related to diagnosis. There is no companion diagnostic required (both CD19 +ve status and CR assessment are routine in ALL-treating centers. It is unlikely that relevant misdiagnosis in this regard occurs in clinical practice. It is not possible to identify responding vs. non-responding patients. All patients should receive blinatumomab.

5.3 What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

The use of blinatumomab in consolidation would not change currently established practices of ongoing disease management and follow-up. Patients receiving blinatumomab would also be receiving current standard chemotherapy and corticosteroids. Patient follow-up would thus remain the same as it currently is for patients receiving only chemotherapy and corticosteroids.

All patients would continue to be followed for disease relapse as they currently are. The outcomes approach used in clinical practice is identical to that of the E1910 study. MRD-ve patients would be expected to remain MRD-ve. MRD+ve patients would be expected to become MRD-ve, and possibly proceed to alloSCT as per current practice. Post blinatumomab patients will continue to be seen and assessed carefully every 1-3 weeks for another ~1 ½ years. Bone marrow MRD assessment varies across Canada, but ongoing MRD analysis may occur as frequently as every three months.

A clinically meaningful response to treatment would be longer remission duration, reduced rates of disease relapse, and longer overall survival, compared to historical chemotherapy-only controls. These endpoints will take several years to realize. If MRD analysis is considered a surrogate marker of clinical response, one would expect patients to remain MRD -ve more durably than is currently seen with chemotherapy alone.

If blinatumomab given during consolidation leads to a reduction in chemotherapy and corticosteroid requirements, and possibly to a shortening of treatment duration (this is very likely to occur with ongoing protocol development), then one would also expect blinatumomab-treated patients to experience less toxicity and morbidity, and an improved QoL. These effects should be particularly marked in elderly patients, who are less able to tolerate conventional chemotherapy than are younger patients.

5.4 What factors should be considered when deciding to discontinue treatment with the drug under review?

By analogy with the E1910 study, Blinatumomab given during consolidation would be planned for a fixed number of cycles only. Once these cycles are completed, there would be no further drug given. Blinatumomab would be discontinued if disease progression (e.g. disease relapse) were to occur during blinatumomab treatment. Blinatumomab might also be discontinued should a severe grade adverse event occur that might be attributable to blinatumomab. These might include very severe cytokine release syndrome, or a neurological event, but these would be extraordinarily rare in patients in CR, and consistent with this, such events were not observed in E1910.

5.5 What settings are appropriate for treatment with [drug under review]? Is a specialist required to diagnose, treat, and monitor patients who might receive [drug under review]?

Blinatumomab is currently given only in academic acute leukemia centers that are experienced in blinatumomab use. In such centers, blinatumomab can be given both in the inpatient and in the outpatient setting. This leukemia center requirement is unlikely to change in the foreseeable future. Specialists involved would be mostly Hematologists (but some Medical Oncologists as well).

6. Additional Information

Blinatumomab given during consolidation (regardless of MRD status) as in the E1910 study defines a new standard of care for B-ALL treatment. It is essential that Canadian patients obtain access to blinatumomab given during intensification.

The chemotherapy backbone used in the E1910 study (derived from the older E2993 protocol) is not one that is commonly used in Canada. Indeed, some current chemotherapy protocols used in Canada are considered superior to E2993. It is thus important that approval for blinatumomab for this new indication is ‘chemo backbone agnostic’, and merely specifies that it should be given in consolidation (i.e. in CR post intensive induction chemotherapy) in CD19+ve B-ALL.

The previously-approved blinatumomab for MRD positivity indication (see 3. above) uses an MRD level of $\geq 10^{-3}$ to define MRD positivity. The world-wide accepted value for defining MRD positivity has long been $\geq 10^{-4}$ however, and it this value ($\geq 10^{-4}$ vs $<10^{-4}$) that defined the MRD+ve and MRD-ve groups in the E1910 study. This is just mentioned for clarification. The older value of $\geq 10^{-3}$ is obsolete.

7. Conflict of Interest Declarations

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

1. Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

   NOT APPLICABLE

2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

   NOT APPLICABLE

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. **Please note that this is required for <u>each clinician</u> who contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

Declaration for Clinician 1

Name: Andre Schuh
Position: Professor of Medicine, University of Toronto; and Hematologist, Princess Margaret Cancer Centre, Toronto
Date: 11.11.2024

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 1: Conflict of Interest Declaration for Clinician 1

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
AbbVie		x		
Amgen		x		
Astellas	x			
AZD	x			
BMS	x			
GlycoMimetics	x			
Jazz	x			
J&J	x			
Kite/Gilead	x			
Loxo	x			
Novartis	x			
Paladin	x			
Pfizer	x			
Servier		x		
Syndax	x			
Teva	x			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 2

Name: Yasser Abou Mourad
Position: Associate Professor, Medicine, UBC; Hematologist, VGH, Vancouver
Date: 14.11.24

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 2: Conflict of Interest Declaration for Clinician 2

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Pfizer		x		
Amgen		x		
Paladin	x			
Jazz		x		
Daiichi-Sankyo	x			
Kite	x			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 3

Name: Mary Lynn Savoie
Position: Clinical Associate Professor, University of Calgary, Division of Hematologic Malignancies Arthur EJ Child Comprehensive Cancer Centre
Date: 11-Nov-2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 3: Conflict of Interest Declaration for Clinician 3

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Novartis			X	
BMS/Celgene	X			
Amgen			X	
Servier	X			
Jazz	X			

Declaration for Clinician 4

Name: Joseph Brandwein
Position: Staff Hematologist and Professor, University of Alberta, Edmonton, AB
Date: 20-11-2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 3: Conflict of Interest Declaration for Clinician 4

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Amgen	X			
Astellas	X			
BMS	X			
Pfizer	X			
Abbvie	X			
Daiichi Sankyo	X			
Servier	X			
Jazz	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 5

Name: David Sanford
Position: Hematologist, Leukemia/Bone Marrow Transplant Program of BC
Date: 20-Nov-2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 3: Conflict of Interest Declaration for Clinician 5

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Astellas	X			
Abbvie	X			
Pfizer	X			
Bristol Myers Squibb	X			
Jazz	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 6

Name: Waleed Sabry
Position: Hematologist, Saskatoon Cancer Center. Professor Hemato-Oncology, University of Saskatchewan.
Date: 20/11/2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 3: Conflict of Interest Declaration for Clinician 6

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Incyte	X			
GSK	X			
Novartis	X			
Janssen	X			
JAZZ		X		
Beigene		X		

* Place an X in the appropriate dollar range cells for each company.

.

Declaration for Clinician 7

Name: Brian Leber
Position: Professor of Medicine (Hematology) , McMaster University; Hematologist, Juravinskl Hospital/Cancer Centre of Hamilton Health Sciences
Date: 11-11-2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 3: Conflict of Interest Declaration for Clinician 7

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Pfizer		x		
Abbvie		x		
Novartis		x		
BMS/Celgene		x		
Servier		x		
AMGEN		x		
Jazz		x		
Astellas		x		
Astex	x			
Paladin	x			
Alexion/GSK		x		
Roche	x			
SOBI		x		
Janssen	x			
Otsuka	x			
Treadwell	x			
Takeda	x			
Taiho	x			

CADTH

CADTH Reimbursement Review

Clinician Group Input

CADTH Project Number: PC0365-000
Generic Drug Name (Brand Name): blinatumomab
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
Name of Clinician Group: OH (CCO) Hematology Cancer Dug Advisory Committee
Author of Submission: Dr. Tom Kouroukis and members of OH-CCO Hematology Cancer Dug Advisory Committee

1. About Your Clinician Group

OH-CCO's Drug Advisory Committees provide timely evidence-based clinical and health system guidance on drug-related issues in support of CCO's mandate, including the Provincial Drug Reimbursement Programs (PDRP) and the Systemic Treatment Program.

2. Information Gathering

Information was gathered via video-conferencing and emails.

3. Current Treatments and Treatment Goals

Other than existing consolidation treatments, there are no other new consolidating agents available. In selected patients ASCT may be considered as part of consolidation.

Goals are to improve survival, reduce relapse and need for second line therapies.

4. Treatment Gaps (unmet needs)

4.1. Considering the treatment goals in Section 3, please describe goals (needs) that are not being met by currently available treatments.

Despite being MRD negative, patients will still relapse, and thus more therapy is required at relapse.

This treatment could decrease the chance of requiring CAR-T or allogeneic transplant.

5. Place in Therapy

5.1. How would the drug under review fit into the current treatment paradigm?

This would be an important addition to first line therapy for MRD negative patients as it shows an improvement in OS.

5.2. Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

As per the clinical trial, including all ages as long as physicians observe that they can tolerate blinatumomab.

MRD testing is required and may or may not be available in all laboratories.

5.3 What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

Standard leukemia testing including peripheral blood and bone marrow tests.

5.4 What factors should be considered when deciding to discontinue treatment with the drug under review?

Significant intolerance or relapsed disease.

5.5 What settings are appropriate for treatment with [drug under review]? Is a specialist required to diagnose, treat, and monitor patients who might receive [drug under review]?

Leukemia centers experienced in giving blinatumomab.

6. Additional Information

The Heme DAC is requesting that pERC review whether blinatumomab could be used for relapsed ALL if used for consolidation.

MRD negativity cut-off has changed from 10^{-3} to 10^{-4} (E1910).

There is a current gap in MRD thresholds. For example, current MRD-positive blinatumomab policy in ON uses a cutoff of 10^{-3} and this current indication is using a threshold of 10^{-4}. We would suggest harmonizing the MRD detection threshold to a level of 10^{-4}. Essentially, all ALL patients will get blinatumomab as part of initial therapy.

7. Conflict of Interest Declarations

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1. Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

   OH-CCO provided secretariat support to the group in completing this submission.

2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

   No

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. **Please note that this is required for each clinician who contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

Declaration for Clinician 1

Name: Dr. Tom Kouroukis
Position: Lead, OH (CCO) Hematology Cancer Dug Advisory Committee
Date: 07-11-2024

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 1: Conflict of Interest Declaration for Clinician 1

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Add company name				
Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 2

Name: Dr. Christopher Cipkar
Position: Member, OH (CCO) Hematology Cancer Dug Advisory Committee
Date: 07-11-2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 2: Conflict of Interest Declaration for Clinician 2

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Add company name				
Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 3

Name: Rami El-Sharkaway
Position: Member, OH (CCO) Hematology Cancer Dug Advisory Committee
Date: 07-11-2024

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Table 3: Conflict of Interest Declaration for Clinician 3

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Add company name				
Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 4

Name: Dr. Joanna Graczyk
Position: Member, OH (CCO) Hematology Cancer Dug Advisory Committee
Date: 07-11-2024

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Table 4: Conflict of Interest Declaration for Clinician 4

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Add company name				
Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 5

Name: Dr. Selay Lam

Position: Member, OH (CCO) Hematology Cancer Dug Advisory Committee
Date: 07-11-2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 5

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Amgen	X			
Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 6

Name: Dr. Lee Mozessohn
Position: Member, OH (CCO) Hematology Cancer Dug Advisory Committee
Date: 07-11-2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 6: Conflict of Interest Declaration for Clinician 6

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Add company name				
Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

CADTH

CADTH Reimbursement Review

Clinician Group Input

CADTH Project Number: PC0365-000
Generic Drug Name (Brand Name): 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.
Name of Clinician Group: Pediatric Oncology Group of Ontario
Author of Submission: Dr. Paul Gibson

1. About Your Clinician Group

POGO is a collaboration of Ontario's five specialized childhood cancer centres and the official advisor to the Ministry of Health and Long-Term Care on pediatric cancer care and control. This submission represents a collaboration of pediatric cancer clinicians from across the province, with membership informed by POGO's Therapeutic and Technology Advisory Committee (TAC). For more information on POGO, please visit www.pogo.ca

2. Information Gathering

This submission was prepared in a consultative manner. Dr. Gibson discussed the indication with members of the submission panel and sought input from POGO's Technology and Therapeutic Advisory Committee (TAC). Dr. Gibson subsequently drafted the initial response, and TAC members or their delegates contributing to the submission reviewed and edited the draft, leading to this final submission. Of note, multiple Ontario clinicians involved in the direct planning and execution of COG AALL 1731 were excluded from the process.

3. Current Treatments and Treatment Goals

Pediatric Acute Lymphoblastic Leukemia (ALL) is the most common pediatric malignancy. Approximately 80% of all new cases of ALL are of B lineage (B-ALL). Upfront B-ALL is treated primarily by risk-stratified, multi-agent chemotherapy. In Ontario and most of Canada, pediatric B-ALL patients are enrolled in clinical trials or treated as per protocols developed and refined by the Children's Oncology Group (COG). A small proportion of newly diagnosed patients may also receive cranial radiation, allogeneic stem cell transplant, and/or cellular therapies. B-ALL therapy has been a model for success in pediatric cancer, with continuous improvement in outcomes because of iterative clinical trials (Raetz, PBC, 2023). Despite these successes, relapsed B-ALL remains a common challenge in pediatric oncology. Thankfully, effective relapse therapies exist, including allogeneic stem cell transplant and cellular therapies. However, relapse therapies carry significant toxicity and leave young patients with a wide variety of potential lifelong late effects. Therefore, the goal in treating pediatric B-ALL is the avoidance of recurrence.

Current multi-agent chemotherapy regimens have been refined over decades with the goal of matching the intensity of cytotoxic therapy to the overall risk of recurrence. It has become clear in recent years, however, that the addition of more intensive cytotoxic therapy (such as etoposide or clofarabine) adds toxicity without improving survival (Salzer, Cancer, 2018). It is clear, therefore, that to minimize recurrence, new agents are needed. Recent results from the E1910 and Children's Oncology Group AALL 1731 clinical trials have clearly shown that these improved outcomes can be achieved by incorporating blinatumomab into intensive chemotherapy regimens for most children and adolescents with B-ALL. Crucially, we suggest this indication should be broadened to include blinatumomab funding as standard of care therapy in infants (van der Sluis, NEJM, 2023) and in patients with Philadelphia Chromosome positive (Ph+'ve) ALL (Foa, NEJM, 2020; Foa, JCO, 2024). Given the overwhelming evidence in E1910 and AALL

1731, it is extremely unlikely that future trials in these small populations will ethically tolerate a randomized blinatumomab question given the strong evidence base that currently exists. It is critical, therefore, that this review does not ignore these patients with rare subtypes.

4. Treatment Gaps (unmet needs)

4.1. Considering the treatment goals in Section 3, please describe goals (needs) that are not being met by currently available treatments.

Apart from a select group of patients with B-ALL risk-stratified as 'Standard Risk Favourable', who have exceptional outcomes with chemotherapy alone, all other patients will benefit from augmentation of current therapy to lower the risk of recurrence. Standard Risk Favourable (patients diagnosed between the ages of 1 and 10 years, with white blood cell counts less than 50 and with favourable cytogenetic lesions and Minimal Residual Disease Negative at the end of a 4-week induction) have been shown to have Event-Free Survival of more than 98% (Schore, Leukemia, 2023). All other risk groups have worse outcomes that require therapy augmentation to avoid relapse and ultimately maximize survival.

Any further augmentation of the current multi-agent chemotherapy approach must have a tolerable side effect profile. As mentioned above, efforts to add further cytotoxic therapy to the standard backbone increased toxicity without improving outcomes. Blinatumomab fills this niche in an important manner. Firstly, it is not a cytotoxic agent and therefore allows concurrent intensive multi-agent anti-neoplastic intensity without compounding the current short- and long-term toxicities of other therapies. Secondly, it may in fact allow cytotoxic 'breaks' in therapy to facilitate recovery from cytotoxic-associated complications such as fungal disease.

5. Place in Therapy

5.1. How would the drug under review fit into the current treatment paradigm?

As previously described, avoidance of recurrence remains the primary goal in the treatment of B-ALL. Both E1910 and AALL 1731 show clear benefits to blinatumomab being added in the front line. Apart from Standard Risk Favourable patients, the standard of care treatment regimen for all newly diagnosed pediatric patients with B-ALL should include blinatumomab as part of multi-agent chemotherapy with the goal of achieving a long-term cure while avoiding toxicities associated with recurrence and stem cell transplant.

The immunotherapy mechanism of action of blinatumomab is distinct and complementary to the traditional cytotoxic backbone. While previous studies have shown important activity in relapsed and refractory circumstances, the known short- and long-term toxicities associated with relapse therapy make the need for upfront use clear. Furthermore, while the current submission suggests use in Philadelphia Chromosome negative B-ALL, we strongly suggest that the sum of the evidence across pediatrics and adult studies suggests that it should be used in Ph+'ve patients also.

The near-universal inclusion of blinatumomab in upfront B-ALL therapy represents a new paradigm of therapy in bringing immunotherapy to augment current multi-agent cytotoxic regimens, resulting in fewer recurrences and reducing the number of patients requiring allogeneic stem cell transplants and/or cellular therapies.

5.2. Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

Blinatumomab targets CD19, a ubiquitous antigen on newly diagnosed B-ALL. To that end, essentially all newly diagnosed B-ALL patients are expected to be eligible for therapy. Any patient with a significant risk of relapse needs this intervention. Those patients with an excellent prognosis on cytotoxic therapy alone (Standard Risk Favourable, as defined above) have less need than all other B-ALL patients. Identification of the select group of patients with standard risk favourable disease is done at the end of induction, as it includes the measure of response (MRD). Of note, all the testing modalities required to risk stratify patients, including identification of those with standard risk favourable disease, are currently in use and accessible to treating pediatric centres.

5.3 What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

Blinatumomab is most effective when incorporated following the initial period of treatment with conventional chemotherapy. To that end, many patients will already be in an MRD-negative state at the time of treatment. Clinical efficacy, therefore, will be shown over time with fewer relapses overall. AALL 1731 studied upfront blinatumomab use in Standard Risk B-ALL. The improved relapse-free survival in these patients aligns with the clinically important outcome. Those patients are typical of those seen in practice. Importantly, the study allowed patients with higher risk features that arise during therapy, namely MRD positivity, to continue on study. Blinatumomab showed impressive activity when added to an augmented backbone in these higher-risk patients.

5.4 What factors should be considered when deciding to discontinue treatment with the drug under review?

The two primary toxicities of blinatumomab are Cytokine Release Syndrome (CRS) and neurotoxicity. These toxicities are rare and usually of lower grades of severity when blinatumomab is incorporated into multi-agent chemotherapy regimens, specifically when the disease burden is low. While both toxicities can commonly be managed by pausing the infusion and using therapies such as dexamethasone and tocilizumab, there are rare patients who either do not tolerate rechallenges post-toxicity or may refuse further treatment. In these settings, blinatumomab should be discontinued, and the patient should continue to be treated with other available therapies.

5.5 What settings are appropriate for treatment with blinatumomab? Is a specialist required to diagnose, treat, and monitor patients who might receive blinatumomab?

Blinatumomab therapy should be initiated under the care of a centre specialized in pediatric oncology. Following its initiation, however, patients who tolerate the infusion can have the ‘bag changes’ required for continuous infusion handled in community hospitals and clinics, provided the training and reimbursement can be facilitated. Importantly, any treating facility must have the pharmacy skill and knowledge to prepare the infusions for CADD pump administration. Furthermore, staff must have a good working knowledge of the pumps to facilitate administration and troubleshooting.

6. Additional Information

As mentioned previously, the proposed indication excludes patients with Philadelphia Chromosome positive (Ph+) ALL. Given the evidence of blinatumomab’s activity across B-ALL subtypes, we strongly urge that the scope of this review be widened to include Ph+'ve B-ALL. With clear activity across the spectrum of B-ALL, we think it is unlikely (and potentially unethical) to await further study in a specific subtype of B-ALL

Future reimbursement strategies for blinatumomab must include consideration of drug wastage. There are three primary mechanisms of wastage. The first is the extra drug needed to prime and fill the line from the pump to the patient. In Ontario, this is currently accounted for in reimbursement. Secondly, there is wastage of vial contents left over after preparing an infusion. This is very common in pediatrics, where patients are unlikely to require ‘full adult dose’ preparations. This is currently not reimbursed. Finally, there is drug lost due to unplanned infusion interruptions (infusion pauses for toxicity management, CADD pump failure, infusion tubing cracking or disconnection, etc.). This is a practical concern in giving this medication, and reimbursement strategies should acknowledge it. Fulsome reimbursement that includes wastage is crucial to ensure equitable access to this therapy across jurisdictions.

7. Conflict of Interest Declarations

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

1. Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

   No

2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

   No

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. **Please note that this is required for each clinician who contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

Declaration for Clinician 1

Name: Dr. Paul Gibson
Position: Pediatric Oncologist, McMaster Children's Hospital, Associate Medical Director, POGO
Date: 14-11-2024

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 1: Conflict of Interest Declaration for Clinician 1

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Add company name				
Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 2

Name: Ms. Stephanie Cox
Position: Nurse practitioner, McMaster Children's Hospital
Date: 14-11-2024

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 2: Conflict of Interest Declaration for Clinician 2

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Add company name				
Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 3

Name: Dr. Donna Johnston
Position: Pediatric Oncologist, Children's Hospital of Eastern Ontario
Date:13-11-2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 3: Conflict of Interest Declaration for Clinician 3

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Jazz Pharmaceuticals	X			
Alexion Pharmaceuticals	X			
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 4

Name: Dr. Salah Ali
Position: Pediatric Oncologist, Kingston Health Sciences Centre
Date: 14-11-2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 4: Conflict of Interest Declaration for Clinician 4

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Add company name				
Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 5

Name: Dr. Sarah Alexander
Position: Pediatric Oncologist, The Hospital for Sick Children
Date: 15-11-2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 5

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Add company name				
Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 6

Name: Dr. Vicky Breakey
Position: Pediatric Oncologist, McMaster Children's Hospital
Date: 16-11-2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 6: Conflict of Interest Declaration for Clinician 6

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Add company name				
Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 7

Name: Dr. Laura Wheaton
Position: Pediatric Oncologist, Kingston Health Sciences Centre
Date: 16-11-2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 7: Conflict of Interest Declaration for Clinician 7

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Add company name				
Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 8

Name: Dr. Alexandra Zorzi
Position: Pediatric Oncologist, Children's Hospital, London Health Sciences Centre
Date: 16-11-2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 8: Conflict of Interest Declaration for Clinician 8

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Add company name				
Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 9

Name: Ms. Paula MacDonald
Position: Pediatric Clinical Pharmacist, McMaster Children's Hospital
Date: 18-11-2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 9: Conflict of Interest Declaration for Clinician 9

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Add company name				
Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 10

Name: Ms. Alicia Koo
Position: Pediatric Clinical Pharmacist, The Hospital for Sick Children
Date: 18-11-2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 10: Conflict of Interest Declaration for Clinician 10

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Add company name				
Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 11

Name: Ms. Tejinder Bains
Position: Pediatric Clinical Pharmacist, Children's Hospital of Eastern Ontario
Date: 18-11-2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 11: Conflict of Interest Declaration for Clinician 11

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Add company name				
Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.