pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Blinatumomab (Blincyto) for Pediatric Acute Lymphoblastic Leukemia

August 23, 2017

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INQUIRIES

Inquiries and correspondence about the pan-Canadian Oncology Drug Review (pCODR) should be directed to:

pan-Canadian Oncology Drug Review
154 University Avenue, Suite 300
Toronto, ON
M5H 3Y9

Telephone: 613-226-2553
Toll Free: 1-866-988-1444
Fax: 1-866-662-1778
Email: requests@cadth.ca
Website: www.cadth.ca/pcodr

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1 GUIDANCE IN BRIEF

This Clinical Guidance Report was prepared to assist the pCODR Expert Review Committee (pERC) in making recommendations to guide funding decisions made by the provincial and territorial Ministries of Health and provincial cancer agencies regarding blinatumomab (Blincyto) for pediatric ALL. The Clinical Guidance Report is one source of information that is considered in the *pERC Deliberative Framework*. The *pERC Deliberative Framework* is available on the CADTH website (www.cadth.ca/pcodr).

This Clinical Guidance is based on: a systematic review of the literature blinatumomab (Blincyto) for ALL conducted by the pediatric Leukemia Clinical Guidance Panel (CGP) and the pCODR Methods Team; input from patient advocacy groups; input from the Provincial Advisory Group; input from Registered Clinicians; and supplemental issues relevant to the implementation of a funding decision.

The systematic review and supplemental issues are fully reported in Sections 6 and 7. A background Clinical Information provided by the CGP, a summary of submitted Patient Advocacy Group Input on blinatumomab (Blincyto) for ALL, a summary of submitted Provincial Advisory Group Input on blinatumomab (Blincyto) for ALL and a summary of submitted Registered Clinician Input on blinatumomab (Blincyto) for ALL and are provided in Sections 2, 3, 4, and 5 respectively.

1.1 Introduction

The purpose of this review is to evaluate the safety and efficacy of blinatumomab as a monotherapy for the treatment of pediatric patients with Philadelphia chromosome-negative (Ph-) relapsed or refractory (R/R) B precursor acute lymphoblastic leukemia (ALL). Health Canada issued a Notice of Compliance with conditions (NOC/c) for Blinatumomab (Blincyto) for the use in pediatric patients for the treatment of Philadelphia chromosome-negative relapsed or refractory B-cell precursor acute lymphoblastic leukemia in April 2017. The funding request is for any relapse at any point in time. For the purpose of this review, relapse is defined as any marrow relapse after allogeneic hematopoietic stem cell transplant (HSCT) or second or later bone marrow relapse. Refractory to other treatments is defined as patients who have not achieved a first remission and have failed a full standard induction regimen, or patients in the first relapse who have failed to achieve a complete remission following full standard reinduction chemotherapy of at least four weeks in duration.

Blinatumomab is administered as a continuous intravenous infusion delivered at a constant flow rate using an infusion pump. A single cycle of treatment is 4 weeks of continuous IV infusion. Each cycle of treatment is separated by a two week treatment-free interval. Patients achieving a complete response (CR) within the first two treatment cycles could receive up to three additional cycles of blinatumomab (5-cycle maximum). The available strength is 38.5 μg lyophilized powder for solution for infusion. Dosing of blinatumomab is based on body weight. For patients less than 45 kg (body surface area-based dose) Cycle 1 is as follows:

- Day 1-7: 5 μg/m^2/day (not to exceed 9 μg/day);
- Day 8-28: 15 μg/m^2/day (not to exceed 28 μg/day).

Subsequent cycles are as follows:

- Day 1-28: 15 μg/m^2/day (not to exceed 28 μg/day).

For patients greater than or equal to 45 kg (fixed dose), Cycle 1 is as follows:

- Day 1-7: 9 μg/day and then Day 8-28: 28 μg/day.
- Subsequent cycles are as follows:
- Day 1-28: 28 μg/day.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

One non-randomized, open-label, single-group phase 1/2 trial was identified that met the selection criteria of this review.[1] Trial MT103-205 evaluated blinatumomab in pediatric and adolescent patients with relapsed or refractory B-cell precursor ALL. The trial was conducted in 26 academic centres in the United States and Europe. No Canadian patients participated in the trial. Patients were treated with blinatumomab between January 30, 2012 and June 3, 2014 and then followed for a two-year period until trial completion (May 24, 2016).

The trial enrolled patients <18 years of age, with a Karnofsky or Lansky performance status of ≥50%, who had B-cell precursor ALL with >25% bone marrow blasts that was either primary refractory, in first relapse after full standard reinduction chemotherapy, in second or later relapse, or any relapse after allogeneic HSCT. Philadelphia chromosome negative or positive patients were eligible for the trial. The key trial exclusions were patients who had active acute or extensive graft versus host disease after HSCT, active CNS or testicular involvement, and previous treatment with blinatumomab.

The Sponsor, Amgen, funded the trial, and oversaw its conduct.

The primary outcome of the trial was the proportion of patients with a complete remission (CR), including patients with complete or incomplete recovery of peripheral blood counts (PBC), within the first two treatment cycles (i.e., 12 weeks). A CR was defined as no evidence of circulating blasts or extramedullary disease and <5% blasts in the bone marrow (M1). The trial was deemed a success if the null hypothesis, a CR ≤10%, was rejected thereby accepting the alternate hypothesis of a CR of 27.5%. At a 5% level of significance, 40 patients were required to provide 80% power to reject the null hypothesis.

The secondary outcomes of interest were the proportion of patients undergoing allogeneic HSCT after blinatumomab treatment, time-to-hematological relapse (i.e., CR duration), overall survival (OS), relapse-free survival (RFS), and safety. Minimal residual disease (MRD) response and complete MRD response were exploratory endpoints, and were defined as $<10^{-4}$ detectable blasts and no detectable blasts, respectively. Quality of life was not assessed in the trial.

All outcomes were appropriately assessed based on intention-to-treat (ITT). However, the phase 2 efficacy results were reported separately (from phase 1) for the primary outcome and only one secondary outcome (i.e., proportion of patients undergoing HSCT). The analyses of OS, RFS, safety, and patient subgroup analyses of the primary outcome included all patients who received the recommended dose of blinatumomab in both phase 1 and phase 2 (i.e., pooled analyses). The pooled analyses were pre-planned but exploratory in nature. No data were reported on time-to-hematological relapse (i.e., CR duration). The criteria of this review required mixed design clinical trials report efficacy results separately by phase. Therefore, data requests were made to the Submitter for the key secondary outcomes that were not reported separately. Refer to Section 6 for a summary of the pooled data analyses.

The phase 1 portion of the trial established stepwise 5/15μg/m^2/d as the recommended dose of blinatumomab for the phase 2 portion. Treatment with blinatumomab was administered as a four-week continuous infusion followed by two weeks off treatment, and involved step-wise dosing of a lower dose (5 μg/m^2) for the first week of the first treatment cycle followed by a higher dose (15 μg/m^2) the remaining three weeks of cycle

1 and subsequent cycles. Patients achieving a CR within the first two treatment cycles could receive up to three additional cycles of blinatumomab (5-cycle maximum).

The MT103-205 trial enrolled and treated 44 patients in the phase 2 portion of the trial. The median age of patients was 10.5 years and the majority of patients were treated in European centres (71%), male (73%), white (75%), had at least two relapses (50%), previous allogeneic HSCT (57%), and were refractory to prior treatment (59%). The median time between last relapse and first infusion of blinatumomab was 1.9 months. A small percentage of patients had genetic abnormalities (including Constitutional trisomy 21) (16%). The previous treatment history of patients was not reported. A request was made to the Submitter for these data, however, they provided only raw data, which precluded a meaningful assessment of this variable.

The majority of patients received blinatumomab for one treatment cycle (93%), with much fewer patients (≤25%) receiving additional cycles of treatment. At the time of primary analysis (January 12, 2015), no patients had completed the two-year follow-up period, and 61% (n=27) had discontinued treatment because of death (n=25) or withdrawal from the trial (n=2). The Submitter confirmed the main causes of death were disease progression (n=12) and multi-organ failure (n=4).[2]

Key Limitations:

- The results of the MT103-205 trial are limited by the level of evidence and lack of randomized, comparative efficacy data for blinatumomab compared to an appropriate comparator regimen (e.g., chemotherapy). Therefore, attributing efficacy and safety events to blinatumomab is difficult since all patients received the same treatment. The trial is also at risk of biases inherent to observational design (e.g., patient selection/ascertainment bias) that can affect a trial's internal validity.
- The trial publication did not provide data on the previous treatment history of patients; therefore, the impact of prior treatments on the outcomes obtained is unknown.
- The trial publication suffers from incomplete reporting of outcomes, as pooled analyses, which were exploratory analyses of the trial, were the focus of the trial publication and the analysis of key secondary outcomes (phase 2) were omitted.
- The results of patient subgroup analyses should be interpreted with caution since they were exploratory and therefore unadjusted for multiple testing (i.e. type 1 error), and many subgroups included small numbers of patients, which calls into question the validity and precision of the estimates obtained.
- The trial did not collect data on health-related QOL; thus the direction and degree to which blinatumomab affects patient-reported QOL parameters in pediatric/adolescent patients with relapsed/refractory B-cell precursor ALL are unknown.

The key efficacy outcomes of the MT103-205 trial are summarized in Table 1.

Table 1: Highlights of key efficacy outcomes in trial MT103-205[1] evaluating blinatumomab in pediatric/adolescent patients with refractory or relapsed B-cell precursor ALL.

Key Efficacy Outcomes[a]	All patients in phase 2 of trial MT103-205 (n=44)[1]		
	No. patients	%	95% CI
Primary CR within first two treatment cycles[b]	14	32	19-48
M1 marrow, full recovery of PBC[c]	6	14	5-27
M1 marrow, incomplete recovery of PBC[d]	5	11	4-25
M1 marrow, neither full nor incomplete recovery of PBC	3	7	1-19
No response (did not achieve a CR):	30	68	NR
Partial remission[e]	3	7	NR
Blast-free hypoplastic or aplastic bone marrow	0	0	NR
Progressive disease[f]	8	18	NR
No response	14	32	NR
No response assessment[g]	5	11	NR
CR within first two treatment cycles by baseline bone marrow blast count			
<50% blasts at baseline	5/12	42	15-72
≥50% blasts at baseline	9/32	28	14-47
Secondary Ability to proceed to HSCT			
Patients who received alloHSCT	13	30	NR
Patients in blinatumomab-induced CR	5	11	NR
Patients in CR who received only blinatumomab	2	5	NR
Non-responders who received subsequent treatment	8	18	NR
Relapse or death after CR[h]	10/14	71	NR
Median time-to-hematological relapse in months (includes only responders)	**Median**	**95% CI**	
	3.4[2]	1.7-NE[2]	
Relapse-free survival (includes only responders)	3.4[2]	1.7-13.9[2]	
Overall survival	8.2	4.0-14.6[i]	

Abbreviations: alloHSCT - allogeneic hematopoietic stem cell transplant; CI - confidence interval; CR - complete remission; HSCT - hematopoietic stem cell transplant; MRD - minimal residual disease; NR - not reported; PBC - peripheral blood count.

Notes:
* All patients treated at stepwise dosage of 5/15 $\mu g/m^2/d$.
[a] Based on the primary analysis on January 12, 2015.
[b] CR defined as no evidence of circulating blasts or extra-medullary disease, and M1 bone marrow (<5% blasts in bone marrow).
[c] M1 marrow (<5% blasts in bone marrow) with platelets >$100x10^9$/L and absolute neutrophil count >$1.0x10^9$/L.
[d] M1 marrow (<5% blasts in bone marrow) with platelets >$50x10^9$/L and absolute neutrophil count ≤$100x10^9$/L, and platelets ≤$100x10^9$/L or absolute neutrophil count ≤$1.0x10^9$/L.
[e] Complete disappearance of circulating blasts and achievement of M2 marrow status (≥5% <25% blast cells) and appearance of normal progenitor cells.
[f] An increase of at least 25%, or an absolute increase of at least 5000 cells/µl (whichever is greater) in the number of circulating leukemia cells, development of extramedullary disease, or other laboratory or clinical evidence of progressive disease.
[g] Patients died (n=5) or withdrew consent (n=1) prior to first response assessment.
[h] Relapse during the efficacy follow-up period with no chemotherapy or alloHSCT between end of blinatumomab treatment and relapse.
[i] Based on analysis at completion of trial (May 24, 2016).

Assessment of AEs was carried out on all patients from phase 1 and 2 (n=70) who received any infusion of blinatumomab at the recommended dose of 5/15 μg/m^2/day during the treatment period and up to 30 days after the last infusion of blinatumomab or before HSCT or the start of chemotherapy. The most common AEs due to any cause were pyrexia (80%), anemia (41%), nausea (33%), and headache (30%). The most frequent grade ≥3 AEs were primarily cytopenias, and included anemia (36%), thrombocytopenia (21%), neutropenia (17%), and febrile neutropenia (17%). Liver function parameters, including ALT (n=13), AST (n=10) and blood bilirubin (n=4), were elevated in 39% (n=27) of patients. Six patients (9%) experienced fatal AEs, of which three died post-allogeneic HSCT after blinatumomab-induced remission. These deaths were preceded by multiorgan failure, sepsis, and respiratory failure.

Treatment-emergent AEs (TEAEs)[2] occurred in all patients (all grade, 100%; grade ≥3, 87%) and serious TEAEs occurred in 56% of patients (grade ≥3, 28%) with the most frequent being pyrexia (11%), febrile neutropenia (11%), and neurologic events (7%) that included convulsions, confusional state, atonic seizures and neuralgia. Eight patients (11%) experienced fatal TEAEs; these deaths were preceded by multiorgan failure, sepsis, fungal infection, recurrent leukemia, disease progression, respiratory failure, and thrombocytopenia. TEAEs lead to treatment interruption in 14% (n=10) of patients and discontinuation of study drug in 6% (n=4) of patients; with two discontinuations deemed treatment-related (due to grade 3 and 4 CRS). In 84% of patients TEAEs were judged related to treatment with blinatumomab (54% were grade ≥3). There were no fatal treatment-related TREAs in the trial.

Cytokine-release syndrome of any grade occurred in 8 of the 70 patients (11%). The worst grade observed was grade 3 in 4% (n=3) of patients and grade 4 in 1% (n=1), which lasted a median duration of 6.5 days (95% CI, 5.0-16.0). Treatment was either interrupted (n=2) or permanently discontinued (n=2) in these patients; however, all four achieved a CR at the 12-week response assessment.

1.2.2 Additional Evidence

See Section 3, Section 4, and Section 5 for a complete summary of patient advocacy group input, Provincial Advisory Group (PAG) Input, and Registered Clinician Input, respectively.

Patient Advocacy Group Input

From a patient's perspective, relapsed and refractory disease often presents with pain and fatigue. One of the most challenging limitations of treatment for newly diagnosed, refractory or relapsed cancer is immunosuppression. Being more susceptible to illness limits interactions with others and limits a child and family's ability to participate in activities outside of the home. Treatment for relapsed and refractory pediatric ALL can involve standard chemotherapy using a variety of drug therapies, stem-cell transplant, radiation, targeted therapies, and other new anti-cancer agents. Side effects from current therapy noted by respondents included: mood changes, neuropathy, pain, nausea/vomiting, hyperactive/hypoactive, loss of appetite, overeating, depression/sadness, gastrointestinal tract damage/mucositis, and insomnia, among others. The most important elements that a drug like blinatumomab must manage for patients and their families include: achieving disease remission, followed by stopping disease progression, then managing disease-related symptoms and minimal and/or manageable side effects, as well as quality of life, among others. Patients without experience with blinatumomab would be willing to tolerate a number of different side-effects in relation to this treatment. However, their families feel strongly about having treatment which does

not result in serious long-term effects and side effects that are difficult to manage such as extreme pain.

Provincial Advisory Group (PAG) Input

Input was obtained from five of the nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact the implementation:

Clinical factors:

- New class of drug that fills gap in therapy for relapsed/refractory ALL
- Unusual dosing schedule of 28-day continuous infusion with 2 weeks off
- High rate of toxicities, particularly neurotoxicities, to monitor and treat

Economic factors:

- Complex and highly resource intensive to prepare and administer and rigorous monitoring for toxicities
- Access to treatment an issue since hospitalization required for administration in the first two cycles and proximity to tertiary care centres required
- High cost of drug

Registered Clinician Input

Overall, the clinicians providing input felt that blinatumomab would fill an unmet need for pediatric patients with relapsed or refractory ALL who have no other options. Blinatumomab has a distinct mechanism of action for patients with refractory disease that has failed to respond to conventional chemotherapy and has better tolerability than chemotherapy although the administration schedule is intense.

Summary of Supplemental Questions

- Critical appraisal of historical comparator study 20140228: a retrospective cohort study of reinduction treatment outcome among pediatric patients with relapsed or refractory B-cell precursor ALL

In order to provide a frame of reference for the efficacy of blinatumomab, the Submitter provided pCODR with the results of a historical comparator study (20140228),[2, 23] which aimed to estimate the efficacy of standard of care treatments (e.g., chemotherapy, targeted therapy) in pediatric patients with relapsed/refractory B-cell precursor ALL. Its objective was to estimate complete remission (CR) in the historical cohort, and to develop a weighted CR to serve as an external comparator to the CR estimate obtained in the blinatumomab trial. Secondary objectives included estimating overall survival (OS), relapse-free survival (RFS), event-free survival (EFS), and the receipt of hematopoietic stem cell transplantation (HSCT), as well as weighted estimates of these outcomes to compare to the blinatumomab trial. The study included patients who experienced a qualifying treatment failure between 2005 and 2013 and were treated at clinical sites in the US, Canada, and Australia belonging to the Therapeutic Advances in Childhood Leukemia and Lymphoma (TACL) Consortium. Eligibility criteria and outcome definitions closely aligned with the MT103-205 trial;[1] however, there were significant differences in the distributions of important baseline characteristics between the studies, with the MT103-205 trial having higher proportions of patients with poorer prognosis. To account for these differences, weighted analyses were

performed with outcome estimates weighted to the distributions in the MT103-205 trial for disease stage (primary analysis), and bone marrow blast percentage prior to treatment, prior HSCT, and time from prior chemotherapy or HSCT (ad hoc analyses). A propensity analysis was also performed to control for multiple variables simultaneously. Efficacy estimates were obtained for first and last qualifying salvage, with the latter considered the most appropriate analysis since it most closely resembled patients in the MT103-205 trial.

A total of 121 patients comprised the primary analysis set.[23] Not all efficacy outcomes (i.e., RFS, and receipt of HSCT) could be assessed due to missing data. Data were available for the majority of patients for CR (n= and n=, for first and last salvage, respectively) and for all patients for OS. The primary analysis (weighted for disease stage) obtained a weighted CR of 30% (95% CI, 20-39%)[23] and a weighted median OS of months ( ) for last qualifying salvage. The ad-hoc analysis (weighted for prior HSCT, baseline bone marrow blasts, and time from prior chemotherapy or HSCT, but not disease stage) obtained a weighted CR of ( ) and a weighted median OS of months ( ) for last qualifying salvage. *Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until August 1, 2018 or until notification by manufacturer that it can be publicly disclosed, whichever is earlier*.) For the propensity score analysis, the primary analysis of OS . (*Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until August 1, 2018 or until notification by manufacturer that it can be publicly disclosed, whichever is earlier*.) Limitations with these analyses raise concerns about its usefulness and validity. Specifically, the overall usefulness of the estimates obtained in the weighted analyses is questionable since they are likely confounded having only been adjusted for the influence of a few and not all important variables. Further, the performance status and previous treatment history of patients were not controlled for in any of the analyses performed, and therefore their influence on the results obtained is unknown. Although a synopsis of the propensity score analysis was provided by the Submitter, there was insufficient reporting of details of the methods used for the analysis, making it difficult to judge the utility and validity of the results. The historical study also likely suffers from low power since the number of included patients was much lower than the required sample size (n=). *Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until August 1, 2018 or until notification by manufacturer that it can be publicly disclosed, whichever is earlier*.) For a comprehensive review of the study and its limitations, refer to Section 7.1.

Comparison with Other Literature

1.2.3 The Clinical Guidance Panel (CGP) identified two relevant studies investigating blinatumomab in the pediatric ALL setting. See Section 8 for further details on the comparison with other literature section.

1.2.4 Factors Related to Generalizability of Evidence

Table 2 addresses the generalizability of the evidence and an assessment of the limitations and sources of bias can be found in Sections 6.3.2.1a and 6.3.2.1b (regarding internal validity).

[Table 2]: Assessment of generalizability of evidence for blinatumomab for pediatric Philadelphia (Ph) negative ALL

Domain	Factor	Evidence (MT103-205, phase 2)[1]	Generalizability Question	CGP Assessment of Generalizability
Population	Performance Status	The trial limited eligibility to patients with a Karnofsky or Lansky performance status of ≥50%. The Karnofsky/Lansky performance status determines the functional status of a recipient. Recipient performance status is a critical data field that has been determined to be essential for all outcome-based analyses. The Karnofsky Scale is designed for recipients aged 16 years and older, and the Lansky Scale is designed for recipients one year old to less than 16 years old.	Does performance status limit the interpretation of the trial results (efficacy or toxicity) with respect to the target population?	The clinical trial was restricted to patients with Karnofsky or Lansky performance status of >50%. The CGP agree that only patients with a Karnofsky or Lansky performance status of >50% should be considered to receive blinatumomab.
	Age	The trial limited eligibility to pediatric patients aged <18 years. • Age <2 years: n=2 (5%) • 2-6 years: n=11 (25%) • 7-17 years: n=31 (17%) Subgroup analyses were conducted by age group, but these were exploratory, pooled analyses (phase 1 and 2 data combined).	Does the age restriction in the trial limit the interpretation of the trial results with respect to the target population?	The clinical trial limited eligibility to pediatric patients that were less than 18 years of age. The CGP agree that blinatumomab can be administered to a pediatric patient that is less than 18 years of age.
	Organ dysfunction	The trial limited eligibility to patients with adequate creatinine clearance and liver function.	Does the exclusion of patients with organ dysfunction limit the interpretation of the trial results with respect to the target population?	Patients in the clinical trial were required to have adequate creatinine and liver function. The CGP recommends that blinatumomab be administered to patients with adequate monitoring in the setting of

Domain	Factor	Evidence (MT103-205, phase 2)[1]	Generalizability Question	CGP Assessment of Generalizability
				stable organ dysfunction.
	Extramedullary disease	The trial excluded patients with evidence of CNS or testicular involvement by ALL.	Did the exclusion of patients with certain sites of metastatic disease limit the interpretation of the trial results with respect to the target population?	The CGP agree that blinatumomab should be considered for patients who have CNS or testicular involvement by ALL as long as the bone marrow is also involved at the time of administration. The trial excluded patients with evidence of CNS or testicular involvement by ALL. The CGP note that patients with isolated CNS disease or only extramedullary disease have better outcomes with current treatment protocols (i.e., mulit-drug chemotherapy). However, if these patients relapse, the CGP recommend that these patients should be eligible for blinatumomab.
	Biomarkers	The trial identified both Ph-negative (n=43) and Ph-positive patients (n=1) who were CD19-positive. Other biomarkers were also identified, including: • MLL: n=2 (5%) ○ MLL-AF.t(4;11): n=2 (5%) ○ Other MLL: n=0 • Hypodiploidy: n=3 (7%)	Is the biomarker an effect modifier (i.e., differences in effect based on biomarker status)? Is there a substantial group of patients excluded from the trial to whom the results could be generalized?	The CGP agree that blinatumomab should be restricted to patients with Ph - negative and CD-19 positive ALL. Although there was one Ph-positive patient enrolled in the phase 2 portion of the trial, the CGP note that patients with Ph- positive ALL is out of scope for this review. Patients with MLL,

Domain	Factor	Evidence (MT103-205, phase 2)[1]	Generalizability Question	CGP Assessment of Generalizability
				MLL-AF.t, and hypodiploidy were not excluded from the trial. The CGP note that these biomarkers are indicators of poor response to conventional chemotherapy and as a result, these patients have a higher chance of relapse and would be considered for HSCT in the 1st remission if a suitable donor is available. However, the CGP agree that a patient with Ph-negative CD19 positive ALL with these biomarkers identified should be eligible to receive blinatumomab.
Intervention	Treatment Intent	The intent of treatment is to achieve remission as a bridge to alloHSCT.	Are the results of the treatment generalizable to an alternative treatment intent?	The CGP agree that the intent of treatment with blinatumomab is to induce remission for patients who have not undergone HSCT, as a bridge to HSCT. For patients who relapse post HSCT, depending on the timing of relapse, a patient may be eligible for a second HSCT if a remission is achieved or a bridge to other therapies/clinical trials such as CAR-T cells.
	Line of therapy	For ≥2 relapses or after HSCT	Are the results of the trial generalizable to	The CGP agree that blinatumomab should be considered for

Domain	Factor	Evidence (MT103-205, phase 2)[1]	Generalizability Question	CGP Assessment of Generalizability

		The trial enrolled patients with relapsed/refractory B-cell precursor ALL with >25% bone marrow blasts.
		
		• Refractory: n=26 (59%)
		• Relapsed: n=18 (41%)
		  ○ Previous relapses:
		  0: n=0
		  1: n=22 (50%)
		  2: n=19 (43%)
		  ≥3: n=3 (7%)
		• Previous HSCT
		  Yes: n=25 (57%)
		  No: n=19 (43%)
			other lines of therapy?	patients with relapsed/refractory disease as defined according to the MT103-205 trial.
				
				Specifically, blinatumomab should be considered for patients who have had a second or later bone marrow relapse, or any marrow relapse after allogenic HSCT.
				
				Blinatumomab should be considered for patients who are refractory to other treatments. Refractory is defined as patients who have not achieved a first remission and have failed a full standard induction regimen, or patients in the first relapse who have failed to achieve a complete remission following full standard reinduction chemotherapy of at least four weeks in duration.

Setting	Countries participating in the Trial	The trial was conducted in the US and in countries in Europe. No Canadian patients were enrolled in the trial.	If the trial was conducted in other countries, is there any known difference in the practice pattern between those countries and Canada?	The trial was conducted predominantly in developed countries with comparable health care systems to that of Canada.
	Location of the participating centres	The trial was conducted in academic and tertiary care centres.	If the trial was conducted only in academic centres are the results	The CGP recommends that blinatumomab should be limited to oncology treatment

Domain	Factor	Evidence (MT103-205, phase 2)[1]	Generalizability Question	CGP Assessment of Generalizability
			applicable in the community setting?	centres with appropriate resources to administer and monitor in academic or tertiary-care centres. Centres must be equipped with appropriate resources to administer and monitor blinatumomab. Infusion pumps used to administer blinatumomab must be programmable, lockable, non-elastomeric, and have an alarm. Depending on the resources available at the pediatric centres, patients may need to be treated as an inpatient for the duration of therapy if outpatient resources are not available (e.g., portable infusion pumps, adequate staff).
	Supportive medications, procedures, or care	Dexamethasone or hydroxyurea were recommended for the first 4 days of the first week of treatment, and was used if baseline marrow blasts were >50%. Patients received prophylactic dexamethasone 10mg/m^2, 6 to 12 hours before and 5mg/m^2 within 30 minutes of each infusion start. CNS prophylaxis was administered before treatment, (at day 15 of	Are the results of the trial generalizable to a setting where different supportive medications, procedures, or care are used?	The CGP note that the supportive care agents used in the trial are similar to what would be used in Canada and would be considered standard of care.

Domain	Factor	Evidence (MT103-205, phase 2)[1]	Generalizability Question	CGP Assessment of Generalizability
		cycle 1, and at the day 29 bone marrow assessment). Neurologic events were treated with dexamethasone at 0.2-0.4 mg/kg/d (maximum 24 mg/d) for up to 3 days.		
Abbreviations: ALL - Acute lymphoblastic leukemia; CR - complete remission; HSCT - hematopoietic stem cell transplant; MRD - minimal residual disease; OS - overall survival				

1.2.5 Interpretation

Burden of illness and need

ALL represents the most common childhood malignancy (approximately 30% of all childhood cancers) and with modern treatment protocols pediatric Philadelphia (Ph) negative acute lymphoblastic leukemia (ALL) is curable in as many as 80-90% of cases. For those that are refractory to treatment or relapse within 36 months of achieving a remission, (1st relapse) the only curative treatment is a Hematopoietic stem cell transplant (HSCT). However to proceed to HSCT, a complete remission needs to be achieved. For patients relapsing after 36 months of achieving remission, conventional chemotherapy can result in a cure of up-to 50%, thus in many centers this group of patients do not proceed to HSCT. Combination chemotherapy used to induce a second remission typically consists of four drug induction - Vincristine, L-asparaginase, anthracycline and steroids (Prednisone or dexamethasone). At the end of 4 weeks remission is defined as bone marrow blasts of <5%. Other combinations that are used after this if remission is not achieved include ifosfamide/etoposide +/- carboplatin, high dose MTX based regimes, high dose Ara-C based regimes, clofarabine, or treatment on clinical trials if available such as CAR T-cells. The use of clofarabine might preclude subsequently receiving CAR-T cells due to profound B-cell aplasia.

There is still a subgroup of patients who do poorly such as induction failures, persistent MRD positivity, hypodiploid patients, mixed lineage leukemia (patient has both ALL and AML), and infants (diagnosed at age <1 year and have MLL gene rearrangement 11q23)- their EFS is around 20%.

Survival of relapsed patients who receive conventional salvage chemotherapy depends on the time to relapse from date of diagnosis - relapse <18 months from diagnosis (High risk) around 5-15%, those relapsing between 18-36 months from diagnosis (intermediate risk) 10-40% and those relapsing >36 months from diagnosis (late relapse) is around 50%.

Treatment options for this group of patients is to proceed to Hematopoietic stem cell transplant (HSCT) once a second remission is achieved with the exception of patients with extra medullary disease and late BM relapses, a proportion of whom can be cured with chemotherapy alone. Patients who experience extramedullary relapse (isolated CNS, testicular) do better with conventional chemotherapy salvage regimens with survival ranging from 40-70% based on the site and time to relapse from diagnosis (usually ≥18 months from diagnosis). These patients do not undergo HSCT at 1st relapse.

Overall survival following HSCT is around 50 - 60%. Treatment-related mortality is observed in 10-30% of patients receiving HSCT based on type of donor available for HSCT. The risk of relapse post HSCT is around 30-40%.[3] Patients who relapse after HSCT, induction failures who do not go into remission with conventional chemotherapy, first relapse patients who do not achieve a 2nd remission or relapse prior to getting a HSCT, refractory disease or who suffer a second relapse have a very poor outlook. Survival of this cohort of relapsed/refractory patients is limited, represent a group of patients with an unmet need and for whom newer treatments are needed.

Efficacy Outcomes

MT103-205 was a single phase open label phase 1/2 dose finding and efficacy trial which evaluated the safety and effectiveness of blinatumomab in pediatric/adolescent patients with relapsed or refractory Philadelphia negative B-cell ALL.[1] Relapsed/refractory disease was defined according to the Study MT103-205 trial, as follows: Any marrow relapse after allogenic HSCT; or second or later bone marrow relapse. Refractory to other treatments; Patients in first relapse must have failed to achieve a CR following full standard reinduction chemotherapy regimen of at least 4 weeks duration; Patients who have not achieved a first remission must have failed a full standard induction regimen.

There were 26 patients in phase 1 portion of the trial treated with the recommended dose of blinatumomab, 44 patients were enrolled from 26 European and US centers in phase 2 portion of the trial and thus a total of 70 patients treated in both phases of the trial at the recommended dose. In the phase 2 portion of the trial, the median age of patients was 10.5 years and the majority of patients were treated in European centres (71%), male (73%), white (75%), had at least two relapses (50%), previous allogeneic HSCT (57%), and were refractory to prior treatment (59%). The median time between last relapse and first infusion of blinatumomab was 1.9 months. The CGP note that this is to be expected since these patients have failed previous therapies. Among patients that received the recommended dose of blinatumomab 52% were in second or later relapse.

a) Remission Rates

The primary outcome of the trial was the proportion of patients with a complete remission (CR), including patients with complete or incomplete recovery of peripheral blood counts (PBC), within the first two treatment cycles. At the primary analysis, 32% of patients in Phase 2 trial (n=14/44) achieved a CR compared to 70 pooled (phase1 and 2) analysis patients, 39% (n=27/70) achieved a CR within the first two treatment cycles (12 weeks).

The CR estimates obtained from pre-specified subgroup analyses should be interpreted with caution as sample sizes were small. Given this caution, never the less some conclusions can be drawn from the CR rates among the patient subgroups (from phase 1 and 2 at the recommended dose of blinatumomab) in the MT103-205 trial. The CR rate among patients in their first relapse who did not achieve a CR at the end of their first re-induction therapy (i.e., refractory) was 32%. The CGP note that a reason why the CR rate was lower among these patients can be explained by the fact that these group of patients have failed their 1st re-induction treatment and are therefore likely more resistant to subsequent treatment. The CR rate among patients in the second relapse and third relapse was 48% and 38% respectively. The CR rate for patients with previous HSCT was 48%. The CGP note that this is particularly impressive as patients relapsing after HSCT have a dismal prognosis and depending on the duration of time to relapse post HSCT, some of these patients might be able to undergo a second transplant for a potential cure.

b) Ability to Proceed to HSCT

All patients who achieved a CR in the phase 2 study were eligible to proceed to HSCT. In the phase 2 portion of the study 30% (n=13/44) patients went on to receive HSCT. Of these five (11%) patients were in a blinatumomab-induced CR and two (5%) were in a CR after only receiving blinatumomab. Of interest, there were also eight (18%) non-responders who received subsequent treatment.

Among all patients that received the recommended dose of blinatumomab, 34% of (n=24/70) responders received an HSCT, and of these patients, 13 (19%) were in a blinatumomab-induced CR (patients received blinatumomab and may have received other treatment including HSCT) and 8 (11%) were in CR after receiving blinatumomab only. The 100-day mortality rate among these patients was 25%. There were 11 (16%) non-responders who received subsequent treatment and HSCT.

c) Time-to-Hematological Relapse (Duration of Response)

The median follow-up time of all pooled patients with a CR (n=27) was 11.5 months and the median time-to-hematological relapse was 5.2 months. Among the 27 responders, seven were still in remission, 13 relapsed, and four died due to disease progression and three from other unspecified causes.

d) Relapse-free Survival

At the completion of the trial, median follow-up time of all pooled patients achieving a CR (n=27) was 23.1 months and median RFS was 4.4 months. At six months, the RFS rate was 42%.

e) Overall Survival

At the completion of the trial, the median OS for all 70 pooled patients was 7.5 months after a median follow-up period of 23.8 months. Based on achieving a CR rate of up to 40%, median RFS and median OS duration of 4.4 months and 7.5 months respectively, blinatumomab cannot be considered to be curative but as a bridging treatment to curative therapy such as HSCT.

f) Minimal Residual Disease

Minimal residual disease (MRD) response in patients who achieved CR within the first two treatment cycle was an exploratory outcome. Among all patients that received the recommended dose of blinatumomab, 52% had complete MRD response. The CGP noted that patients who achieved a MRD negative response had better outcomes.

Safety

The most frequent grade ≥3 AEs were primarily cytopenias, including anemia (36%), thrombocytopenia (21%), neutropenia (17%), and febrile neutropenia (17%).

Treatment-emergent AEs (TEAEs) occurred in all patients (all grade, 100%; grade ≥3, 87%) and serious TEAEs occurred in 56% of patients (grade ≥3, 28%) with the most frequent being pyrexia (11%), febrile neutropenia (11%), and neurologic events (7%) that included convulsions, confusional state, atonic seizures and neuralgia. Eight patients (11%) experienced fatal TEAEs.

Cytokine-release syndrome of any grade occurred in 8 of the 70 patients (11%). The worst grade observed was grade 3 in 4% (n=3) of patients and grade 4 in 1% (n=1).

These AEs and SAEs while occurring in the majority of patients were manageable either by stopping blinatumomab temporarily or stopping blinatumomab permanently. The CGP note that cytokine release syndrome is specific to blinatumomab and can be prevented or treated with dexamethasone. Neurological toxicities were reversible on stopping the drug.

Based on this evidence and clinical opinion, the remission rates of blinatumomab are similar to those of standard combination chemotherapy regimens. The toxicities associated with blinatumomab are different than with standard chemotherapy, and do not include the same incidence of infections, which can render patients ineligible for subsequent alloHSCT. However, the only way to definitively confirm this is through a randomized clinical trial. Cytokine release syndrome and neurological toxicities are specific to blinatumomab, both of which can be successfully managed by use of dexamethasone and stopping blinatumomab, respectively. Data on the historical comparator control group provided by the submitter offered a potentially useful comparator against which to evaluate the efficacy and incremental cost effectiveness of blinatumomab in pediatric patients with relapsed and refractory Philadelphia-negative ALL in the absence of a direct comparison within a randomized trial. The historical comparator supplied by the submitter reported a weighted CR rate of 30% and a weighted median OS of [redacted] months. These results [redacted] in the MT103-205 trial. *Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until August 1, 2018 or until notification by manufacturer that it can be publicly disclosed, whichever is earlier*.) However, the CGP and Methods Team identified several weaknesses and limitations inherent to historical comparator data and suggest that caution should be exercised in interpreting the results.

Limitations

- The trial publication did not provide data on the previous treatment history of patients beyond the use of prior alloHSCT, and therefore, the effect of previous treatments received among patients is unknown. The CGP noted that while there is significant heterogeneity in the standard of care treatments that exists for pediatric/adolescent relapsed/refractory B-cell precursor ALL, knowledge of what prior treatments were received among patients is likely not a significant factor for interpreting efficacy results and the generalizability of those results. What is of importance is the disease state at the time of enrollment as it is known that the more relapses a patient has the less likelihood of responding to conventional chemotherapies.
- The trial publication reported pooled analyses from phase 1 and phase 2 to provide a larger sample size for data analysis. These were considered exploratory analyses of the trial and were the analysis of key secondary outcomes.
- The CGP noted that the results of the presented patient subgroup analyses should be interpreted with caution since they were exploratory and many subgroups included small numbers of patients.
- The CGP noted that the trial did not collect data on health-related QOL; thus the direction and degree to which blinatumomab affects patient-reported QOL in pediatric/adolescent patients with relapsed/refractory B-cell precursor ALL are unknown.
- Although not a limitation, it should be noted that the estimation of the trial's sample size (and thus power) was based on rejecting the null hypothesis that a CR within the first two treatment cycles was ≤10% versus the alternate hypothesis of 27.5%. The trial (phase 2 portion) was deemed a success if nine or more patients out of 40 achieved a CR (22.5%). The CGP noted that those success criterion chosen were based on the response rate of clofarabine, a drug not often used currently in the Canadian setting for treating relapsed pediatric ALL patients.

1.3 Conclusions

The Clinical Guidance Panel (CGP) concluded that there may be a net clinical benefit of blinatumomab for the treatment of pediatric patients with Philadelphia chromosome-negative relapsed/refractory B-precursor ALL. This conclusion is based on one phase 1/2 non-randomized study which reported a CR rate of 39% among all patients within 12 weeks of treatment with blinatumomab at the recommended dose and a CR rate of 32% in patients in the phase 2 portion of the trial within 12 weeks of treatment with blinatumomab.

In making this conclusion, the CGP also considered the following:

- An historical control was developed and submitted by the submitter in order to provide a frame of reference for the efficacy of blinatumomab. While conservative estimates of comparative efficacy can be determined through this data, several limitations were identified inherent to the use of this data. Hence caution should be exercised in interpreting these results. The CGP noted that historical comparators are not ideal and a randomised phase III trial would be needed to definitively answer the role of blinatumomab in the pediatric relapsed/refractory ALL setting.
- While subgroup analyses were considered exploratory in nature and were comprised of a small number of patients, the CGP acknowledge the subgroup of patients who relapsed post HSCT achieved a CR rate of 48% (95% CI 32-64) with treatment with blinatumomab, which appears to be a clinically meaningful CR rate in a patient population that is known to have very poor outcomes. This particular subgroup of patients do not have other treatment options and effective therapies are needed following relapse post HSCT. It is unlikely that there will be data from randomized clinical trials to clearly establish the superiority of blinatumomab to standard chemotherapy in the relapse post HSCT pediatric population.
- There is no data on the impact of blinatumomab on quality of life in the pediatric setting.
- The CGP acknowledge recent efforts to make blinatumomab more easily accessible as an outpatient therapy through the use of portable infusion devices contrasted with other treatment options that may require hospital admissions and are important considerations in the face of comparable efficacy in inducing remission. However, although blinatumomab may be given on an outpatient basis, the supportive care and pharmacy requirements for pediatric patients with relapsed/refractory ALL who are receiving this treatment would likely require that patients remain in close proximity of hospital for the duration of therapy. For instance, patients will need access to transfusion support for cytopenias, nursing care for pump maintenance and expedited admissions for complications such as febrile neutropenia, neurological impairment and cytokine release. It is likely that patients would spend at least part of their course of therapy in hospital. Furthermore, pediatric centres that do not have the appropriate outpatient resources to administer and monitor blinatumomab will require patients to be treated in hospital beyond the initial cycle of therapy.
- Cytokine release syndrome and neurological events are specific AEs to blinatumomab. These AEs can be managed and/or are reversible by the prophylactic use of dexamethasone, cyto reductive therapy such as hydroxyurea or stopping blinatumomab when blinatumomab is used as a single agent.
- The use of blinatumomab can be considered as a bridge to other salvage treatment such as allogeneic HSCT.

- An ongoing randomised phase 3 trial of blinatumomab versus standard reinduction chemotherapy backbone, study AALL1331 (NCT02101853)[4] is currently under way by the Children's Oncology Group (estimated primary completion date of April 2018) and is expected to answer definitively the role of blinatumomab in relapsed pediatric ALL.
- While there may be a response to blinatumomab in adults, the scope of this review is only considers pediatric patients less than 18 years of age.

2 BACKGROUND CLINICAL INFORMATION

This section was prepared by the pCODR pediatric Leukemia Clinical Guidance Panel. It is not based on a systematic review of the relevant literature.

2.1 Description of the Condition

Acute Lymphoblastic Leukemia (ALL) is a highly-aggressive hematological malignancy that presents with signs or symptoms of bone marrow failure (fatigue, dyspnea, bleeding, bruising or infection), organ infiltration (testicular disease, central nervous system (CNS)) and systemic complaints (chiefly fevers, fatigue, decreased appetite, weight loss). Patients typically present to hospital acutely ill, often with infections due to neutropenia, electrolyte disturbances related to tumour lysis syndrome or with neurological abnormalities suggestive of CNS disease. The majority of patients have circulating blast at presentation and the diagnosis is confirmed by bone marrow or peripheral histology and ancillary tests like flow cytometry, cytogenetics and immunohistochemistry.

2.2 Accepted Clinical Practice

ALL represents the most common childhood malignancy (approximately 30% of all childhood cancers) and with modern treatment protocols pediatric ALL is curable in as many as 90% of cases.[5] Treatment principles include the use of sequential multi-drug combinations for the treatment of ALL. Agents with activity in ALL induction include vincristine, corticosteroids, methotrexate, anthracyclines and L-Asparaginase. At the time of presentation, patients in North America are classified as standard risk (SR) (total WBC<50,000 x 10^9/L and age 1-10 years).[6] Children over the age of 10 years regardless of WBC are classified as high risk (HR). This classification determines their initial treatment – SR patients receive a 3 drug induction – Vincristine, Dexamethasone and PEG L-Asparaginase. HR patients receive a 4th drug – anthracycline;Prednisone instead of Dexamethasone is given to patients >/= 10 years. Patients who do not have CNS disease (CNS1) receive CNS directed prophylaxis chemotherapy intrathecally (directly inserted into the spinal fluid) to address occult CNS disease. Patients with CNS disease receive extra intrathecal treatments to eradicate CNS disease. Once remission has been achieved which occurs in the majority of patients (95-98%), patients begin the next phase of treatment – Consolidation which may last for between 6-9 months with patients with higher risk disease receiving more intensive and longer treatments followed by a maintenance phase, which may last up to 30 months for some protocols. This can impose significant personal and financial burdens on affected patients and their families.

A number of factors determine prognosis in ALL. Traditionally, age and cytogenetics have been viewed as the most important prognostic factors in ALL. Newer treatment protocols, however, have proven effective across the spectrum of cytogenetic abnormalities and seem to have abrogated some of the risk associated with high-risk cytogenetics in this disease. More recently, Minimal Residual Disease (MRD) has been shown to be a significant prognostic factor in patients with both SR and HR disease as well as those with high risk cytogenetic abnormalities such as hypodiploidy (EFS 38.9% at 8 years) and the presence of Philadelphia chromosome.[3,7,8] Philadelphia chromosome (which results from a balanced translocation between chromosomes 9 and 22) confers sensitivity to tyrosine kinase inhibitors and while Philadelphia-positive ALL cure rates were around 25-30% with conventional treatment, the use of TKI's in combination with chemotherapy has resulted in a 5 year EFS of around 70% and a good quality of life.[9]

The majority of young patients with ALL can expect to be cured with modern chemotherapy protocols. A review done by Pui et al[5] showed that almost 90% of childhood ALL can be cured by modern intensive chemotherapy based on risk assignment at diagnosis and MRD status during induction.

There is still a subgroup of patients who do poorly such as induction failures, persistent MRD positivity, hypodiploid patients, mixed lineage leukemia (patient's leukemia has features of both ALL and AML), and infants (diagnosed at age<1 year with MLL gene rearrangement 11q23)– their EFS is around 20%.

Survival of relapsed patients who receive conventional salvage chemotherapy depends on the time to relapse from date of diagnosis - relapse <18 months from diagnosis (High risk) have a survival rate of around 5-15%, those relapsing between 18-36 months from diagnosis (intermediate risk) 10-40% and those relapsing >36 months from diagnosis (late relapse) is around 50%.[6,10,11]

Treatment options for this group of patients is to proceed to Hematopoietic stem cell transplant (HSCT) once a 2nd remission is achieved with the exception of patients with extra medullary disease and late BM relapses, a proportion of whom can be cured with chemotherapy alone.

Overall survival following HSCT is around 50- 60%. Treatment-related mortality is observed in 10-30% of patients receiving HSCT based on type of donor available for HSCT. The risk of relapse post HSCT is around 30-40%.[12]

Patients who relapse after HSCT, induction failures who do not go into remission with conventional chemotherapy, first relapse patients who do not achieve a 2nd remission or relapse prior to getting a HSCT, refractory disease or who suffer a second relapse have a very poor outlook. Survival of this cohort of relapsed/refractory patients is limited, represent a group of patients with an unmet need and for whom newer treatments are needed.

Patients who achieve 1st remission and subsequently suffer a first relapse less than 36 months from diagnosis are treated with a four drug reinduction protocol – Prednisone or Dexamethasone, Vincristine, Anthracycline and PEG-L-asparaginase for a total duration of 28 days. If a complete remission (so called 2nd remission) is achieved (CR) they proceed to consolidation therapy with a rotating combination of drugs – cyclophosphamide, Ara-C, vincristine, prednisone or dexamethasone, anthracycline, High dose Methotrexate, PEG L-asparaginase, etoposide until they can proceed to a HSCT.

Patients whose 1st bone marrow relapse occurs beyond 36 months or extramedullay relapse beyond 18 months from diagnosis are usually treated with chemotherapy only.

There are many ALL therapy protocols that are based on different combinations of chemotherapy agents used in various doses and schedules. As such, there is no consensus on the current standard of care for the treatment of pediatric patients with Philadelphia chromosome-negative relapsed or refractory B-precursor ALL. However, the majority of North American institutions use the UK ALL R3 regimen for first relapse of childhood ALL, and this regimen also serves as the control arm of the current COG clinical trial for first relapse of childhood ALL (AALL1331).[4] Patients who fail to achieve a 2nd remission (this group of patients + refractory patients is the patient population for whom funding is being requested by the Sponsor) will then go on to other lines of conventional chemotherapy. Chemotherapy combinations that might be used include, but are not limited to cyclophosphamide or ifosfamide with etoposide, High dose Methotrexate, Vincristine, FLAG (fludarabine, Ara C +/- an anthracycline) and clofarabine. Clofarabine is not only expensive but leads to profound B-cell aplasia and with the availability of clinical trials using CAR T-cells and prior treatment with clofarabine being an exclusion criterion, clofarabine is falling out of favour as the availability of treatment with CAR-T cells becomes more wide spread.

Other options at the time of 1st relapse or subsequently is enrollment on a clinical trial e.g. at present the Children's Oncology Group has a randomised relapsed leukemia trial in 1st relapse comparing standard conventional chemotherapy (SCC) vs SCC + Blinatumomab.[4]

Enrollment on a CAR T-cell protocol as a clinical trial is also available at very limited centers in Canada.

2.3 Evidence-Based Considerations for a Funding Population

The management of B-Cell non-Hodgkin lymphoma was revolutionized by the introduction of monoclonal anti-CD20 antibodies into clinical practice. These agents however show only limited activity in ALL. Blinatumomab represents the first immune mediated novel therapeutic agent in Philadelphia-negative ALL. Blinatumomab is a first-in-class bispecific T-Cell engaging (BiTE) antibody construct with sites to engage CD19 expressed on B-ALL tumour cells and CD3 on T-Lymphocytes. By bringing these two cell types into close approximation a T-Cell mediated immune response is simulated, which results in clearance of malignant cells by the redirected immune system. Adverse effects reflect this mechanism of action and include cytokine release syndrome, tumour lysis syndrome, infections and febrile neutropenia.

2.4 Other Patient Populations in Whom the Drug May Be Used

While there is no evidence available to extend the use of blinatumomab into other patient populations, patients with CD19+ diseases such as Philadelphia positive ALL, mixed lineage leukemia could potentially benefit from treatment with blinatumomab. The clinical panel acknowledges that there is no data on the magnitude of benefit in this group and use of blinatumomab should not be put into practice until studies confirming its effectiveness and cost-effectiveness compared to other available alternatives is established.

3 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

Input on blinatumomab (Blincyto) of pediatric patients with Philadelphia chromosome-negative relapsed or refractory B precursor acute lymphoblastic leukemia (ALL) was provided by Advocacy for Canadian Childhood Oncology Research Network (Ac2orn), Leukemia and Lymphoma Society of Canada (LLSC), and Ontario Parents Advocating for Children with Cancer (OPACC) in a joint submission. Their input is summarized below.

Ac2orn, LLSC, and OPACC gathered information through two different surveys, personal experience and one-on-one conversations.

An online survey was posted on Survey Monkey and distributed by Ac2orn and LLSC asking for input from patients who are in treatment or in remission from ALL, and who have experience with blinatumomab. The link to the survey was distributed by email and through social media channels. In this survey, one completed survey was received; this completed survey was from a parent located in Saskatchewan. Five other surveys were started; however, they were not completed after the first question.

A second survey was posted on Survey Monkey by OPACC and distributed through email to their member families as well as through their social media channels. In this survey, there were 10 respondents; all 10 respondents were parents of children with ALL located in Ontario. Seven out of the 10 respondents were female and the rest chose not to identify themselves.

Both surveys addressed questions regarding blinatumomab. The information from both surveys were combined to complete the patient input for this pCODR submission. One one on one interview was conducted with a parent whose child is currently in treatment for relapsed ALL. One family who had direct experience with blinatumomab through a clinical trial responded to the survey.

From a patient's perspective, relapsed and refractory disease often presents with pain and fatigue. One of the most challenging limitations of treatment for newly diagnosed, refractory or relapsed cancer is immunosuppression. Being more susceptible to illness limits interactions with others and limits a child and family's ability to participate in activities outside of the home. This can result in all family members not being able to participate in sports, school, visiting family, and many other activities during the first three phases of treatment. Treatment for relapsed and refractory childhood ALL can involve standard chemotherapy using a variety of drug therapies, stem-cell transplant, radiation, targeted therapies, and other new anti-cancer agents. Side effects from current therapy noted by respondents included: mood changes, neuropathy, pain, nausea/vomiting, hyperactive/hypoactive, loss of appetite, overeating, depression/sadness, gastrointestinal (GI) tract damage/mucositis, and insomnia, among others.

Ac2orn, LLSC, and OPACC reported the following challenges families and patients face: professional and employment challenges, financial issues, marital challenges, mental health, family dynamic, and stress on support networks. According to Ac2orn, LLSC, and OPACC, families and patients are willing to tolerate a wide range of side-effects from treatment as long as the treatment used is effective against the cancer and the child is able to achieve long-term survival. The most important elements that a drug like blinatumomab must manage for patients and their families include: achieving disease remission, followed by stopping disease progression, then managing disease-related symptoms and minimal and/or manageable side effects, as well as quality of life, among others. Patients without experience with blinatumomab would be willing to tolerate a number of different side-effects in relation to this treatment. However, their families feel strongly about having treatment which does not result in serious long-term effects and side effects that are difficult to manage such as

extreme pain. One family who had direct experience with blinatumomab through a clinical trial responded to the survey.

Please see below for a summary of specific input received from Ac2orn, LLSC, and OPACC. Quotes are reproduced as they appeared in the survey, with no modifications made for spelling, punctuation or grammar. The statistical data that are reported have also been reproduced as is according to the submission, without modification.

3.1 Condition and Current Therapy Information

3.1.1 Experiences Patients have with Acute Lymphoblastic Leukemia (Pediatric)

According to Ac2orn, LLSC, and OPACC Philadelphia Chromosome-Negative relapsed or refractory pediatric B precursor Acute Lymphoblastic Leukemia (referred to as ALL in the rest of the document) presents a significant therapeutic challenge.

Ac2orn, LLSC, and OPACC noted that ALL is the most common childhood cancer, and the most common type of leukemia (a blood cancer) that occurs in children. Patients diagnosed with ALL initially experience symptoms such as fever, weakness, pain, enlarged lymph nodes and bruising. When children are initially diagnosed, they are stratified into different risk categories (standard, high, very high risk) based on their age, white blood cell count, whether it is relapsed disease, and based on specific tests such as cytogenic or chromosome tests. Patients experience four different treatment phases that consist of:

Remission Induction Chemotherapy – using chemotherapy such as vincristine, prednisone, asparaginase and possibly others to cause the cancer cells to go into remission. (Approximately 4 to 6 weeks)

Consolidation – treatment given to the central nervous system (CNS) to prevent the spread of the disease to the brain and/or spinal cord. (Approximately 1 to 2 months)

Intensification Therapy – high dose chemotherapy to kill remaining cancer cells. (2 to 6 months)

Maintenance Therapy – use of methotrexate, cercaptopurine, vincristine, dexamethasone and other drugs to maintain remission. (Approximately 3 years)

According to Ac2orn, LLSC, and OPACC, when a patient relapses after frontline therapy or is classified as having refractory disease, the treatment pathway becomes slightly less clear. Without the appropriate treatment, the patient's outcome can be compromised. If the appropriate treatment is not realized or if no treatment is given at all, the disease is 100% fatal.

Ac2orn, LLSC, and OPACC noted that relapsed and refractory disease often presents with pain and fatigue, and it is the treatment of the disease which results in a number of different side-effects.

Ac2orn, LLSC, and OPACC reported that one of the most challenging limitations of treatment for newly diagnosed, refractory or relapsed cancer is immunosuppression (where the child's immune system is weak and unable to fight against possible infections). They stated that being more susceptible to illness limits interactions with others and limits a child and family's ability to participate in activities outside of the home. Ac2orn, LLSC, and OPACC felt that it is an immense challenge to try and protect your child from possible exposures to illness, while trying to maintain some semblance of a normal routine within the family. According to Ac2orn, LLSC, and OPACC, this can result in all family members not being able to participate in sports, school, visiting family, and many other activities during the first three phases of treatment.

3.1.2 Patients' Experiences with Current Therapy for Acute Lymphoblastic Leukemia (Pediatric)

Ac2orn, LLSC, and OPACC noted that there is no standard treatment for relapsed or refractory childhood ALL. According to Ac2orn, LLSC, and OPACC, the type of treatment that a patient will receive for relapsed and/or refractory ALL will depend on many factors:

1. The amount of time that passed in between the completion of treatment and the confirmation of disease recurrence
2. The response to treatment
3. The location of the relapse
4. Genomic based risk factors associated with the disease
5. Other possible factors

Ac2orn, LLSC, and OPACC stated that all of above factors also determine how well a patient will respond to therapy for relapsed pediatric ALL and if they are able to achieve a subsequent remission.

Treatment for relapsed and refractory childhood ALL can involve standard chemotherapy using a variety of drug therapies (vincristine, asparaginase, doxorubicin, cyclophosphamide, etc. - systemic and intrathecal administration), stem-cell transplant (allogeneic, from a donor), radiation (cranial, total body, etc.), targeted therapies (blinatumomab and CAR T-cell therapy), and other new anti-cancer agents.

From the survey, patients with relapsed disease had experience with:

1. Drug therapies (100%)
2. Radiation (10%)
3. Other (20%)

The following side-effects patients experienced from relapsed therapies included:

Side-Effect	Mentions
Mood Changes	4
Neuropathy	3
Pain	3
Nausea/Vomiting	2
Hyperactive/Hypoactive	2
Loss of Appetite	2
Overeating	2
Depression/Sadness	2
GI Tract Damage/Mucositis	2
Insomnia	2
Diarrhea	1
Headache	1
Loss/Gain of Weight	1
Fever	1
Hair Loss	1
Infections	1
Steroid Induced Diabetes	1

Below are quotes from respondents related to challenges with mood changes and steroids:

- *"Our daughter has responded well to all drug therapies, except for a mixture that she is given once a month during the maintenance phase of chemo. She is given IV Vincristine, oral methotrexate, and begins a 5 day dose of 5mg dexamethasone. By the third day, our daughter has severe insomnia, and is screaming in pain from neuropathic pain. For days 3,4 and 5, our daughter can't function normally. She can't sleep, is crying on and off, and cannot go to school due to the neuropathic pain she feels in her whole body. Two days after completing the 5 days of steroids, our daughter returns to normal. Only for this to happen again, a month later. This has been going on since the beginning of maintenance, so the last 5 months. It is horrifying and exhausting to watch my daughter roll on the floor in pain and there is nothing I can do to help. We have tried Naproxen, and Morphine. Nothing works. It takes a toll on the whole family. Her sisters have to watch in fear when I try to calm her down and sit holding her on the floor while I cry because it hurts so much to watch this. She is exhausted for days after the steroids wear off. She misses school every month during this period. It causes her fear of meds, and after being in chemo for over a year, it is difficult to try to get her to take meds that she know will cause horrifying pain."*
- *"When on dexamethasone, his mood swings are high and low. He's constantly hungry. When he gets a Lumber Puncture and IT methotrexate, those days are tough, do to the fatigue and hunger. To time a child for 6MP is difficult as they are unable to eat for 3 hours daily."*
- *"Steroids kept her up so much, rubbed down health caring for her, reprimanded at work for time needed to care for child."*
- *"Steroid induced diabetes; AVN in hip and both shoulders requiring replacement surgeries; mouth sores; heavy dependency on pain meds"*
- *"His legs and back hurt a lot, steroids make him have mood swings, he always has to take a break from not eating and it bothers him."*
- *"Dexamethasone was very difficult on our son. We were somewhat prepared for his intense hunger, constipation and mood swings. But, we none of us were prepared for watching our son transform into a basically un-recognizable child – in his appearance, his physical abilities and in his demeanour. It was heartbreaking and difficult for everyone."*
- *"Coming off of dexamethasone led to full body muscle aches and unbearable pain – screaming and crying for hours."*

Below are quotes from respondents regarding other side-effects and issues related to treatment:

- *"Constant fever, diarrhea, headache, losing and gaining weight, nausea, loss of hair, getting hyperactive and hypoactive. Loss of appetite and over eating as well. Moody sometimes."*
- *"My son experienced drug induced psychosis eventually managed by a mood stabilizing drug. As well as methotrexate toxicity that totally damaged his GI tract/lining and lead to hospitalization for a month. Constant nausea but not vomiting. Vincristine induced neuropathy resulting in mild foot drop."*
- *"Vincristine has caused my child to have neuropathy. He hasn't walked since he was diagnosed 9 months ago. We try to fit physio treatment twice a week. He contracted a fungal infection at the start of his treatment. We feel doctors are doing a great job with selecting the right meds for his fungal infection."*

- *"Our son experiences severe anxiety around having his Port (IV) accessed for chemotherapy, which has been stressful for us as parents, but also problematic for his nurses."*

The following are some quotes from caregivers:

- *"Nausea was well managed by Ondanzetron and the psychosis once diagnosed was managed with Respiradone. Scary before diagnosed. Foot drop was tolerable yet providing PT and getting my son to do the recommended exercises was difficult. The toxicity was horrible and no child or parent caregiving for a child so sick should have to go through that."*

- *I feel I have a high tolerance of side effects. We support our daughter to throw up if she needs to, we don't make a fuss, we just say Good job for getting the yucky stuff out and tell her she doesn't need to cry because she did a great job! Losing hair, fatigue, upset tummy, these are all side effects I expected during chemotherapy. We can tolerate a lot, but pain that I can't stop, or decrease, I can't tolerate."*

- *"Constipation. Fatigue, and anything that wouldn't have long term effects."*

According to Ac2orn, LLSC, and OPACC, within Canada, it is not difficult to access the necessary therapies for treatment for childhood ALL from a medical perspective. However, there are many challenges that families and patients face during this time:

1. Professional and employment challenges (loss of employment, reduction in employment)
2. Financial issues (costs of medications, travel, parking, care for your other children)
3. Marital challenges (separation, divorce, single parenting)
4. Mental health (stress, fear, depression, anxiety, uncertainty)
5. Family dynamic (siblings, grandparents, and extended family members)
6. Stress on support networks (asking for help from friends, neighbours, community)

Ac2orn, LLSC, and OPACC noted that treatment for newly diagnosed childhood ALL takes approximately 4 years from start to finish. If a child relapses, the treatment for relapsed disease can also take a significant amount of time with upwards of an additional 2+ years of therapy. Ac2orn, LLSC, and OPACC submit that this is a serious amount of time for families to be dealing with the myriad of challenges that will face them throughout the treatment journey. It also puts a great deal of strain on the family's support network, and not all families have people that they can rely on to help them with the care of their other children, making meals, and other important assistance needs.

3.1.3 Impact of Acute Lymphoblastic Leukemia (Pediatric) and Current Therapy on Caregivers

According to Ac2orn, LLSC, and OPACC, families and patients are willing to tolerate a wide range of side-effects from treatment as long as the treatment used is effective against the cancer and the child is able to achieve long-term survival. Even if cure is not possible, parents

and families want time. For many families, even for those whose children may not have a favourable outcome, treatment is pursued to try and give the child and family another week, month, holiday, or birthday together. Ac2orn, LLSC, and OPACC submit that time together is critically important for families to have, allowing them to have more experiences together and write the memories of their child into their hearts and minds with indelible ink.

Ac2orn, LLSC, and OPACC noted that there are a wide range of issues that are faced when a child is diagnosed with cancer, and certainly when the child has refractory or relapsed disease. Daily routines, relationships with friends and family, mental health, financial stability, and basic physical functioning are all challenges noted by Ac2orn, LLSC, and OPACC.

Below are quotes from families to illustrate the impact of ALL and current therapy on caregivers:

- *"Became anti-social, forgetting about self care and just focused on my child. Obsession on being germ free."*
- *"Siblings suffer from lack of attention, fear that mommy and daddy will be gone for long periods of time when our daughter is admitted, school attendance, school work, marital relationship, sleeping issues for child and parents."*
- *"Almost bankrupt and ended marriage in divorce."*
- *"We're always living on the edge."*
- *"Worrying was the hardest part. Not just about the future, but about the symptoms: Were the symptoms and complaints "real"?, Is this an indication of relapse? Should we call the on-call oncologist? Do we need to go the Emergency Department? There were so many things to be stressed about.*
- *"As our son's primary caregiver, there were times when I struggled with anxiety and depression. I felt like my emotions were out of control and that I didn't recognize myself anymore. I worried about my ability to return to work.. to ever return to normal."*

3.2 Information about the Drug Being Reviewed

3.2.1 Patient Expectations for and Experiences To Date with Blinatumomab (Blincyto)

The most important elements that a drug like blinatumomab must manage for patients and their families are:

1. Achieving disease remission (100%)
2. Stopping disease progression (88.9%)
3. Managing disease-related symptoms (77.8%)
4. Minimal and/or manageable side effects (77.8%)
5. Quality of life (66.7%)
6. Daily functioning (44.4%)
7. Drug accessibility/drug toleration/stress and mental health/financial burden (33.3% each)

For patients without experience with blinatumomab, they said that they would be willing to tolerate a number of different side-effects in relation to this treatment. However, families

feel strongly about having treatment which does not result in serious long-term effects and side-effects that are difficult to manage such as extreme pain.

Ac2orn, LLSC, and OPACC stated that despite the advances in current therapies, children with relapsed B-lineage ALL have limited treatment options. These children are at a high risk of a subsequent relapse, and have a much higher rate of death from their disease. The use of additional chemotherapies for relapsed disease can result in significant toxicities which can have devastating short and long-term effects. In addition, Ac2orn, LLSC, and OPACC noted that the disease can become resistant to chemotherapy, requiring different modes of action to attack and kill the disease. According to Ac2orn, LLSC, and OPACC, children with relapsed and refractory ALL need additional treatment options that offer a chance at remission, cure, reduced side-effects, and a better overall quality of life.

Ac2orn, LLSC, and OPACC reported that one family who had direct experience with blinatumomab through a clinical trial responded to the survey. Unfortunately, the patient died while receiving this therapy. These were the only details provided by the family.

3.3 Additional Information

None.

4 SUMMARY OF PROVINCIAL ADVOCACY GROUP (PAG) INPUT

Overall Summary

Input was obtained from five of the nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact the implementation:

Clinical factors:

- New class of drug that fills gap in therapy for relapsed/refractory ALL
- Unusual dosing schedule of 28-day continuous infusion with 2 weeks off
- High rate of toxicities, particularly neurotoxicities, to monitor and treat

Economic factors:

- Complex and highly resource intensive to prepare and administer and rigorous monitoring for toxicities
- Access to treatment an issue since hospitalization required for administration in the first two cycles and proximity to tertiary care centres required
- High cost of drug

Please see below for more details.

4.1 Factors Related to Comparators

PAG noted that clinical trial is standard, if available. It was also noted that if first relapse, current standard may be further chemotherapy followed by transplant. If second relapse, standard may be palliative chemotherapy or novel agents if available.

4.2 Factors Related to Patient Population

Blinatumomab would fill the gap in therapy for pediatric patients with relapsed or refractory Philadelphia chromosome negative ALL. PAG identified that the patient population eligible for treatment with blinatumomab should align with the patient population in the trial.

PAG noted that patients with Philadelphia chromosome positive ALL and T-cell ALL would be out of scope of this review.

PAG is seeking guidance on the use of blinatumomab in patients currently receiving salvage therapy for Philadelphia chromosome negative ALL and in patients who have received an allogeneic stem cell transplant and relapsed post stem cell transplantation, on time limited need.

4.3 Factors Related to Dosing

PAG has concerns that the dosage and administration schedule is very unusual. Blinatumomab is administered by continuous infusion for 28 days. PAG indicated that the preparation of the infusion bags is resource and labour intensive and that patients are required to be near a tertiary care centre with the appropriate resources to prepare, administer and monitor for 28 days. This would be a barrier to implementation and access to treatment would be limited to certain centres.

4.4 Factors Related to Implementation Costs

PAG identified that the preparation, administration and monitoring of blinatumomab infusion is very resource intensive due to

- Hospitalization for administration would likely be for 28 days for the first cycle and the first two days of the second cycle
- Pre-medications required prior to first dose of each cycle and whenever infusion is interrupted for more than four hours
- Strict adherence and intensive staff training for the very complex preparation process that includes pre-coating infusion bags with the provided solution stabilizer
- Monitoring and treatment of toxicities
- Multiple clinic visits for infusion bag to be changed and multiple times required to prepare infusion bags in the four week infusion period
- Availability of programmable, lockable infusion pumps

PAG noted there would drug wastage as there is only one vial size of 38.5 μg and the doses are much smaller for pediatric patients weighing less than 45 kg. PAG also noted that overfill is required for the tubing and the initial start-up of the infusion pump.

Since the stability of the reconstituted vials is 24 hours refrigerated and the stability of the prepared infusion bags is 10 days refrigerated, PAG noted that the one vial can be used to prepare more than one infusion bag. However, 5.5mL of stabilizer is required to prepare each infusion bag and there is only 10mL of stabilizer included with each vial of drug. Thus, to prepare additional bags from one vial of drug, additional stabilizer is required from a different package.

4.5 Factors Related to Implementation Costs

Access would be limited to treatment centres with the appropriate resources to administer and monitor. The administration of blinatumomab requires considerable coordination of inpatient care in tertiary hospital and outpatient cancer clinics. In addition, infusion pumps used to administer blinatumomab must be programmable, lockable, non-elastomeric, and have an alarm. PAG noted that this type of pumps are not readily available in all treatment centres.

4.6 Factors Related to Manufacturer

PAG identified the high cost of the drug, the one vial size and the lack of long term data would be barriers to implementation. PAG is seeking information from the manufacturer on whether a smaller vial size would be forthcoming, to minimize wastage for the smaller doses used in pediatric patients, and whether a larger volume of stabilizer would be available to facilitate more than one infusion bag preparation per vial of drug.

5 SUMMARY OF REGISTERED CLINICIAN INPUT

Two registered clinicians provided two individual inputs on blinatumomab for pediatric ALL and their input is summarized below. Overall, the clinicians providing input felt that blinatumomab would fill an unmet need for pediatric patients with relapsed or refractory ALL who have no other options. Blinatumomab has a distinct mechanism of action for patients with refractory disease that has failed to respond to conventional chemotherapy and has better tolerability than chemotherapy although the administration schedule is intense.

Please see below for a summary of specific input received from the registered clinicians.

5.1 Current Treatment(s) for this Type of Cancer

One clinician providing input noted that the current first-line treatment is DFCI consortium 11001 (off study), second-line treatment is the COG AALL1331 (on study) / UK - MRC ALLR3 Protocol (mitoxantrone arm) or Clofarabine+VP16+Cyclophosphamide followed by HSCT (off-study) and third-line treatment is CAR-T therapy.

Another clinician providing input noted that at present, relapse disease is treated with three initial blocks of intense chemotherapy, primarily delivered as inpatients. Factors such as timing of relapse, type of relapse, and treatment response will dictate whether a patient will continue on chemotherapy only or proceed with a stem cell transplant.

The clinician noted that there is no clear optimal therapy for refractory disease. Patients with induction failure or those who have persistent Minimal Residual Disease (MRD) have poor outcomes and the role of traditional chemotherapy is unclear.

5.2 Eligible Patient Population

ALL is the most common pediatric malignancy and blinatumomab would allow patients to receive therapy at relapse with significantly less acute and long term side effects.

One clinician providing input indicated that at this very moment, it is hard to figure the precise patient population for blinatumomab in pediatric patients. Both blinatumomab and anti-CD19 CAR-T target the same population (i.e. relapsed CD19+ ALL). Blinatumomab is presently being tested as first relapse/refractory therapy in the AALL1331 trial (randomization with chemotherapy) and, off-study, is available as compassionate for patients refractory or in second or further relapse. Anti-CD19 CAR-T is available only on-study for patients refractory or in second or further relapse (or relapse after HSCT). Preliminary results from both therapies in children suggest that anti-CD19 CAR-T seems to be more active (i.e. higher CR and longer event-free survival) compared to blinatumomab. On the other hand, it's well known that some patients have comorbidities and/or are unable to collect or manufacture lymphocytes to participate in anti-CD19 CAR-T studies.

In one clinician's point of view that at this time, blinatumomab would be for patients with a CD19+ ALL that are in second or further relapse, are in a refractory relapse or are refractory to two lines of induction of therapy and present comorbidities (not eligible to receive a CAR-T treatment) or are unable to collect/manufacture lymphocytes.

5.3 Identify Key Benefits and Harms with New Drug Under Review

Benefits identified include:

- very few (if any) long-term toxicities compared to chemotherapy;

- probably better tolerated than chemotherapy for patients with most types of comorbidities or active infections than chemotherapy;
- possibility of have most of the treatment as outpatient

Harms identified:

- Continuous 4 week infusion required
- severe short-term neurotoxicity in some patients;
- reversible B-cell aplasia (use of IVIG until B-cell recovery);
- Blinatumomab can limit the use of anti-CD19 CAR-T in case of relapse (specifically if a CD19 negative relapse)

One clinician noted that while the first infusion may be associated with acute inflammatory reaction and significant symptoms, by the fourth or fifth day, the difference in the patients is quite remarkable. Patients do not have the infectious toxicities, require far less transfusion and can spend substantially less time in hospital. Furthermore, the patients avoids alkylator and topoisomerase inhibitor exposure to lessen the chances of late effects on fertility and endocrine and second malignancy.

5.4 Advantages of New Drug Under Review Over Current Treatments

The clinicians providing input noted that blinatumomab provides comparable clinical outcomes in the primary relapse setting and is at least as effective as conventional therapy for patients in second or further relapsed or refractory disease. They indicated that blinatumomab is associated with less toxicities, has far less infection complications and end organ damage. In addition, blinatumomab reduces the need for hospitalizations and transfusions and can be an interesting bridge to allogeneic HSCT. Comparing to CAR-T therapy, blinatumomab is less active but can be offered in some situations where the patient is not eligible or unable to have lymphocytes for gene manipulation for CAR-T production. Blinatumomab has a distinct mechanism of action for patients with refractory disease that has failed to respond to conventional chemotherapy.

5.5 Sequencing and Priority of Treatments with New Drug Under Review

The clinicians providing input noted that blinatumomab can replace conventional therapy in relapsed and refractory disease. Blinatumomab would ideally be included as part of re-induction for all relapsed precursor B ALL patients and could be used as a bridge to allogeneic HSCT.

For refractory disease, blinatumomab would be suitable for those pre-B ALL patients who have failed induction therapy or patients whose MRD remains positive after consolidation.

5.6 Companion Diagnostic Testing

The clinicians providing input indicated that almost all patients with B-cell ALL express CD19 antigen. As flow cytometry is a standard of care to identify patients without CD19 expression. Thus a new companion diagnostic test is not required for blinatumomab.

5.7 Additional Information

One clinician providing input noted a profound difference in quality of life in children who have received blinatumomab compared to traditional chemotherapy. The patients are active and in ambulatory care compared to prolonged hospitalization.

6 SYSTEMATIC REVIEW

6.1 Objectives

To evaluate the efficacy and safety of blinatumomab as monotherapy for the treatment of pediatric patients with Philadelphia chromosome-negative (Ph-) relapsed or refractory B-precursor acute lymphoblastic leukemia (ALL). For the purpose of this review, relapsed or refractory B-cell precursor ALL are defined as follows:

- Relapsed B-precursor ALL includes patients in second or later bone marrow relapse, or any marrow relapse after allogeneic hematopoietic stem cell transplant (HSCT).
- Refractory B-precursor ALL includes patients who have not achieved a first remission and have failed a full standard induction regimen, or patients in first relapse who have failed to achieve a complete remission following full standard reinduction chemotherapy of at least four weeks in duration.

A supplemental question relevant to the pCODR review and to the Provincial Advisory Group was identified while developing the review protocol and is outlined in Section 7.1.

- Critical appraisal of historical comparator study 20140228: a retrospective cohort study of re-induction treatment outcomes among pediatric patients with relapsed or refractory B-cell acute lymphoblastic leukemia.

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

Table 3. Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Published or unpublished RCTs In the absence of RCTs, fully published non-comparative clinical trials evaluating blinatumomab**	Pediatric patients (aged <18 years) with Ph-negative relapsed or refractory B-cell precursor ALL	Blinatumomab administered as a continuous iv infusion delivered at a constant flow rate using an infusion pump	No consensus on current standard of care Acceptable chemotherapy includes but is not limited to: • Vincristine/l'asparaginase /anthracycline/steroids • Ifosfamide/etoposide ± carboplatin • High-dose methotrexate-based regimens • High-dose cytarabine + anthracycline • CAR-T-cells/ionotuzumab as part of a clinical trial • Clofarabine	• **Hematologic response (CR)** • CR duration • Time-to-hematological relapse • Proportion of patients undergoing HSCT • OS • RFS • MRD response/complete MRD response • Safety • **Quality of life**
Abbreviations: ALL - Acute lymphoblastic leukemia; CR - complete remission; HSCT - hematopoietic stem cell transplant; MRD - minimal residual disease; OS - overall survival; Ph - Philadelphia Chromosome; RFS - relapse-free survival.				
Notes: * Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions) in combination with supportive care.				

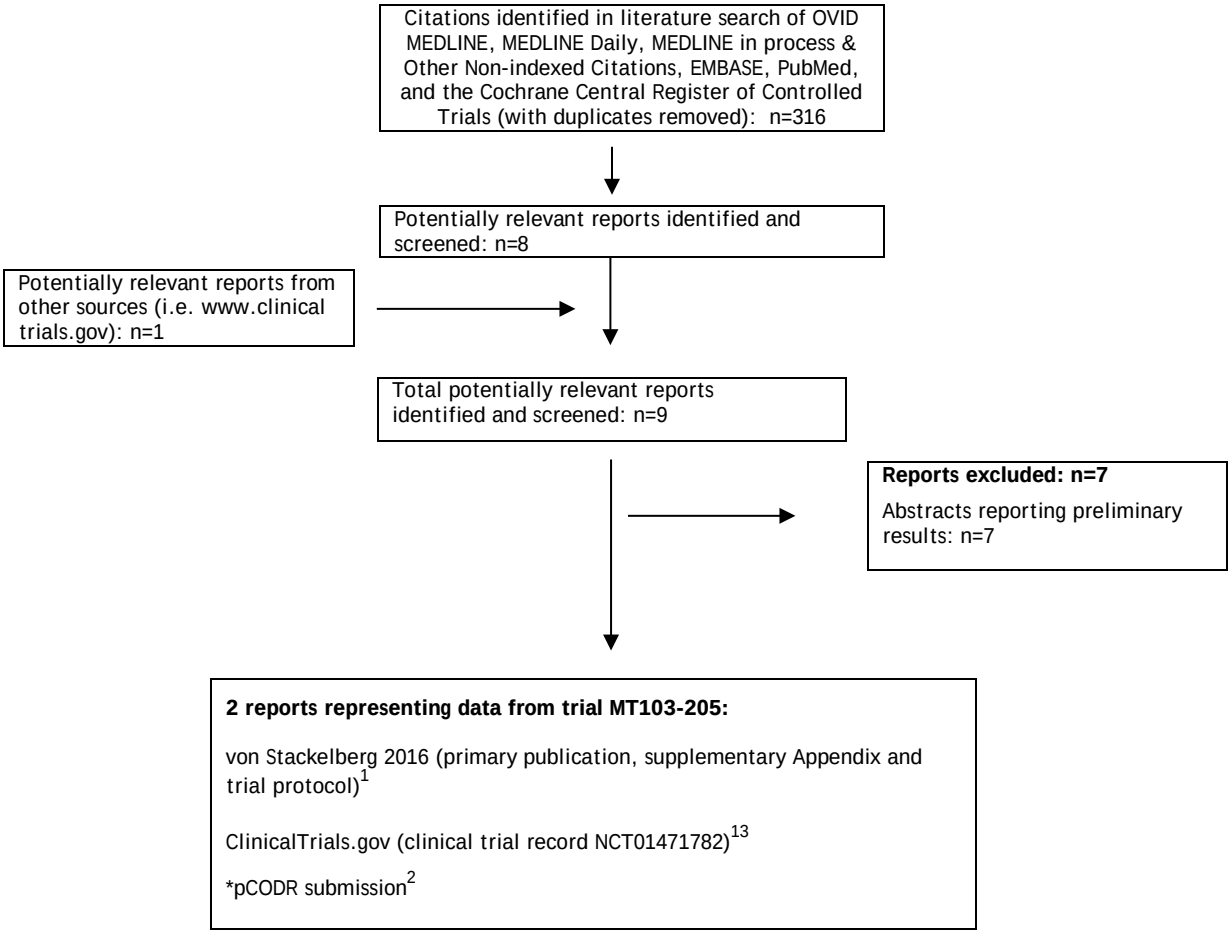
**Dose escalation trials were excluded but mixed design clinical trials (i.e. trials with a dose escalation phase followed by an efficacy-determining phase in which the intervention is administered at the same dose and schedule to all patients) were included if data were reported separately for the two phases of the trial.

6.3 Results

6.3.1 Literature Search Results

Of the nine potentially relevant reports identified, two reports representing one unique trial were included in the pCODR systematic review,[1,13] and seven reports were excluded. The seven reports were excluded because they were abstracts of the included trial reporting preliminary trial results.[14-20]

Figure 1: QUOROM Flow Diagram for Inclusion and Exclusion of Studies



**Note: Additional data related to the MT103-205 trial were also obtained through requests to the Submitter by pCODR.*

6.3.2 Summary of Included Studies

One non-randomized, open-label, single-group phase 1/2 trial was identified that met the selection criteria of this review.[1] Trial MT103-205 evaluated blinatumomab in pediatric and adolescent patients with B-cell precursor ALL that was refractory, in second or later relapse, and/or in relapse after allogeneic HSCT. Key characteristics of the trial are summarized in Table 4 and specific aspects of trial quality are summarized in Table 5.

6.3.2.1 Detailed Trial Characteristics

Table 4. Key trial characteristics of included trial MT103-205[1] evaluating blinatumomab in pediatric/adolescent patients with refractory or relapsed B-cell precursor ALL.

Trial Design	Key Eligibility Criteria	Intervention	Trial Outcomes
Von Stackelberg 2016[1] (MT103-205) Single-group, open-label, phase 2 clinical trial N treated=44 26 European and US centres Patient enrolment dates: January 2012-June 2014 Data cut-off for primary analysis: January 12, 2015 Funded by Amgen	Inclusion Criteria: • Age <18 years • BCP-ALL with >25% bone marrow blasts • Refractory/relapsed disease, including: o Primary refractory[a] o In first relapse after full salvage induction regimen[b] o In second or later relapse o Any relapse after allogeneic HSCT • Karnofsky or Lansky (age <16 years) PS of ≥50% • Philadelphia chromosome negative or positive • Adequate creatinine clearance and liver function • Informed consent Exclusion Criteria: • Active acute or extensive chronic graft-versus-host disease after HSCT • Active or extensive CNS or testicular involvement • Previous treatment with blinatumomab • Any HSCT within three months prior to receiving blinatumomab treatment	Blinatumomab administered as a continuous iv infusion at a constant flow rate at dose of 5/15 $\mu g/m^2/d$[c] for four weeks followed by two weeks off, for up to five cycles[d]	Primary: • CR rate within first two treatment cycles[e] Secondary: • AE incidence • Proportion of patients undergoing HSCT after blinatumomab treatment • Time-to-hematological relapse (CR duration) • RFS • OS Exploratory: • MRD response rate • Complete MRD response rate

Abbreviations: AE - adverse events; BCP-ALL - B-cell precursor acute lymphoblastic leukemia; CR - complete remission; HSCT - hematopoietic stem-cell transplant; MRD - minimal residual disease; OS - overall survival; RFS - relapse-free survival; iv - intravenous.

Notes:
[a] Patients who had not achieved a first remission must have failed a full standard induction regimen.
[b] Patients in first relapse must have failed to achieve a complete remission following full standard reinduction chemotherapy of at least four weeks in duration.
[c] The lower dose of blinatumomab was administered for the first week of the first treatment cycle followed by the higher dose for the remaining three weeks and subsequent cycles.

Infusion was administered in the hospital for the first week of the first cycle and during the first two days of the second cycle. Remaining cycles were done in the outpatient setting.
[d] Patients achieving a complete remission within the first two treatment cycles of blinatumomab could receive up to three additional consolidation cycles or be withdrawn from treatment to receive consolidation chemotherapy or HSCT at the investigator's discretion.
[e] CR includes patients with incomplete recovery of peripheral blood counts.

Table 5. Quality features of trial MT103-205 (phase 2)[1] evaluating blinatumomab in pediatric/adolescent patients with refractory or relapsed B-cell precursor ALL.

Trial	Treatment vs. Comparator	Primary Outcome	Required Sample Size	Sample Size	Randomization Method	Allocation Concealment	Blinding	ITT Analysis	Final Analysis	Early Termination	Ethics Approval
von Stackelberg 2016[1] (MT103-205)	Blinatumomab No comparator	CR rate within first two treatment cycles[a]	40 patients[b] were required to provide 80% power to reject the null hypothesis of a CR rate within the first two cycles of ≤10%, and detect a CR of 27.5% using a two-sided significance level of α=0.05	44	NA	NA	NA	Yes	Yes	No	Yes

Abbreviations: CR = complete response; ITT - intent-to-treat; NA - not applicable.

Notes:
[a] The best response within the first two treatment cycles was used to determine efficacy.
[b] Patients were enrolled using a Simon-like two-stage design. In stage 1, 21 patients were enrolled and received the recommended dose of blinatumomab. If more than two patients achieved a CR, an additional 19 patients were enrolled into stage 2. The trial was declared successful, if at the end of the study, nine or more patients (phase 2 portion of the study) had a response.

a) Trials

Trial MT103-205 was a non-comparative, open-label, phase 1/2 dose-finding and efficacy trial conducted in 26 academic centres in the United States and Europe.[1] No Canadian patients participated in the trial. Patients were treated with blinatumomab between January 30, 2012 and June 3, 2014 and then followed for a two-year period until trial completion (May 24, 2016).

The trial enrolled pediatric and adolescent patients <18 years of age, with a Karnofsky or Lansky performance status of ≥50%, who had B-cell precursor ALL with >25% bone marrow blasts that was either primary refractory, in first relapse after full standard reinduction chemotherapy, in second or later relapse, or any relapse after allogeneic HSCT. Philadelphia chromosome negative or positive patients were eligible for the trial. The key trial exclusions were patients who had active acute or extensive graft versus host disease after HSCT, active CNS or testicular involvement, and previous treatment with blinatumomab. Refer to Table 4 for a comprehensive list of the key eligibility criteria used in the trial.

The Sponsor, Amgen, funded the trial, and oversaw its conduct. Eleven of the 23 trial authors disclosed potential conflicts of interest that included compensation from the Sponsor for honoraria, consulting/advisory roles, employment, stock ownership, and travel and accommodation expenses.

The primary outcome of the trial was the proportion of patients with a complete remission (CR), including patients with complete or incomplete recovery of peripheral blood counts (PBC), within the first two treatment cycles (i.e., 12 weeks). A CR was defined as no evidence of circulating blasts or extramedullary disease and <5% blasts in the bone marrow (M1). The secondary outcomes of interest were the proportion of patients undergoing allogeneic HSCT after blinatumomab treatment, time-to-hematological relapse (i.e., CR duration), overall survival (OS), relapse-free survival (RFS), and safety. Minimal residual disease (MRD) response and complete MRD response were exploratory endpoints, and were defined as $<10^{-4}$ detectable blasts and no detectable blasts, respectively. All time-to-event outcomes were assessed using the methods of Kaplan-Meier using appropriate censoring. Quality of life was not assessed in the trial.

Hematologic response to treatment, which was assessed locally and verified by central review, was determined by bone marrow aspiration and/or biopsy during screening, at day 15 of cycle 2, and at the end of each 28-day treatment cycle. MRD response was assessed by central review.

Information on aspects of trial quality, including sample size considerations, is summarized in Table 5. All outcomes were appropriately assessed based on intention-to-treat (ITT). In the primary trial publication, the phase 2 efficacy results were reported separately (from phase 1) for the primary outcome and only one secondary outcome (i.e., proportion of patients undergoing HSCT). The analyses of OS, RFS, safety, and patient subgroup analyses of the primary outcome included all patients who received the recommended dose of blinatumomab in both phase 1 and phase 2 (i.e., pooled analyses). According to the trial protocol, the primary efficacy analyses were to be carried out on patients from the phase 2 portion of the trial, and pooled analyses with phase 1 data were pre-planned but exploratory in nature. No data were reported in the trial publication on time-to-hematological relapse (i.e., CR duration). The trial was considered an exploratory study, so no adjustments for multiplicity were made in efficacy analyses.

The phase 1 portion of the trial established stepwise 5/15μg/m^2/d as the recommended dose of blinatumomab for the phase 2 portion. There were 26 patients in phase 1 treated with the recommended dose of blinatumomab, and thus a total of 70 patients treated in both phases of the trial at the recommended dose. The criteria of this review required mixed design clinical trials report efficacy results separately by phase. Therefore, data requests were made to the Submitter for the key secondary outcomes that were not reported separately. However, in light of the small sample size of the phase 2 portion (n=44), the identical blinatumomab dosing design and inclusion criteria, and the fact that pooled analyses were pre-planned (albeit exploratory) and used for Health Canada regulatory submissions, the pooled data have been included in this report for reference but the primary focus of the report are the phase 2 results.

b) Populations

Phase 2

The MT103-205 trial enrolled and treated 44 patients in the phase 2 portion of the trial. The baseline characteristics of treated patients are summarized in Table 6. The median age of patients was 10.5 years and the majority of patients were treated in European centres (71%), male (73%), white (75%), had at least one relapse (50%), previous allogeneic HSCT (57%), and were refractory to prior treatment (59%). The median time between last relapse and first infusion of blinatumomab was 1.9 months. A small percentage of patients had genetic abnormalities (16%). The previous treatment history of patients was not reported. A request was made to the Submitter for these data, however, they provided only raw data, which precluded a meaningful assessment of this variable.

Pooled Analysis (Phase 1 and 2)

Compared to patients in phase 2 only, there were higher percentages of patients aged <2 years (14% versus 5%), white (87%[2, 13] versus 75%), and with genetic abnormalities (26%), and a lower percentage of patients aged 7-17 years (57% versus 71%) in the pooled analysis (Table 6).

c) Interventions

Phase 2

Treatment with blinatumomab was administered as a four-week continuous infusion followed by two weeks off treatment, and involved step-wise dosing of a lower dose (5 μg/m^2) for the first week of the first treatment cycle followed by a higher dose (15 μg/m^2) the remaining three weeks of cycle 1 and subsequent cycles. Treatment was administered in hospital for the first week of cycle 1 and during the first two days of cycle 2, and then switched to an outpatient setting for remaining cycles. Patients achieving a CR within the first two treatment cycles could receive up to three additional cycles of blinatumomab (5-cycle maximum). Retreatment with blinatumomab (at the recommended dose) was permitted for patients who relapsed after achieving a CR of at least three months in duration.

Blinatumomab was discontinued permanently if patients experienced any of the following: adverse events (AEs) meeting the criteria for dose-limiting toxicities

(DLT)[a], a neurologic event requiring more than one week to resolve to grade ≤1, disease progression or hematologic/extramedullary relapse, treatment interruption/delay of greater than two weeks, or more than two treatment discontinuations for AEs within one treatment cycle. For non-DLT AEs causing treatment interruption, treatment could be restarted at one dose lower after resolution to grade ≤1.

Prophylactic dexamethasone (or hydroxyurea) was advised for patients (and was required for patients with baseline blast counts >50%) for four days during the first week of treatment to prevent cytokine release syndrome (CRS); doses were administered six to 12 hours (10 mg/m^2) and 30 minutes (5 mg/m^2) prior to each infusion start. CNS prophylaxis was also administered at age-adjusted doses on day 15 of cycle 1 and on the day 29 bone marrow assessment; and neurologic events were treated for up to three days at doses between 0.2 and 0.4 mg/kg/d (up to 24 mg/d maximum).

Among the 44 phase 2 patients the median duration of treatment with blinatumomab (i.e., during the whole infusion period excluding retreatment) was 28 days (range, 9.9 to 146.4) and the median absolute cumulative dose[b] received by patients was 349.88 μg (range, 79.78 to 2126.03).[2] One patient received retreatment, and the outcomes of this patient were analysed with the other patients in the trial.

Pooled Analysis (Phase 1 and 2)

Among the 70 patients treated in the pooled analysis, the median duration of treatment with blinatumomab during the whole infusion period was 28 days (range, 3.4 to 146.4) and the median absolute cumulative dose[b] received by patients was 349.89 μg (range, 15.86 to 2126.03).[2]

d) Patient Disposition

Phase 2

The disposition of patients in the MT103-205 trial is summarized in Table 7. All enrolled patients were treated (n=44) and included in the primary analysis of CR. The majority of patients received blinatumomab for one treatment cycle (93%), with much fewer patients (≤25%) receiving additional cycles of treatment. At the time of primary analysis (January 12, 2015), no patients had completed the two-year follow-up period, and 61% (n=27) had discontinued treatment because of death (n=25) or withdrawal from the trial (n=2). The Submitter confirmed the main causes of death were disease progression (n=12) and multi-organ failure (n=4).[2]

Information on protocol deviations that occurred during the course of the trial was not reported in the trial publication. A request was made to the Submitter for this information, and they indicated [redacted]% (n=[redacted]) of patients deviated from the trial protocol.[2] *Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until August 1, 2018 or until notification by manufacturer that it can be publicly disclosed, whichever is earlier*.) The deviations that took place related to the enrolment of patients with ≥25% blasts in bone marrow (M3) at trial entry

[a] The dose limiting toxicities observed in cycle 1 of phase 1 of the trial were grade 4 CRS (n=3, with one attributed to grade 5 cardiac failure) and grade 5 respiratory failure (n=1).
[b] Total exposure in μg for each patient varied according to their body surface area.

([redacted]%, n=[redacted]), timing of assessments ([redacted]%, n=[redacted]), and the length of the treatment-free interval between cycles ([redacted]%, n=[redacted]).[2] *Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until August 1, 2018 or until notification by manufacturer that it can be publicly disclosed, whichever is earlier*.) The nature of these deviations did not exclude patients from efficacy analyses.

Pool Analysis (Phase 1 and 2)

The disposition of the 70 patients in the pooled analysis treated at the recommended dose of blinatumomab was similar to that of phase 2 patients, with the exception of slightly higher percentages of patients completing two treatment cycles of blinatumomab (31% versus 25%) and discontinuing treatment (70% versus 61%) (Table 7). The types of protocol deviations that took place among the 70 patients were similar in nature to those occurring in the phase 2 patients (see above), but they occurred slightly more frequently (17.1%, n=12).[2]

At the end of the trial, the percentage of patients completing the two-year follow-up period was 20% (n=14), with the majority of study discontinuations (n=56, 80%) due to death (n=48, 69%).

e) Limitations/Sources of Bias

Refer to Table 5 for a summary of quality-related features of the MT103-205 trial (phase 2).

Overall, the results of the MT103-205 trial are limited by the level of evidence, and lack of randomized, comparative efficacy data for blinatumomab compared to an appropriate comparator regimen (e.g., chemotherapy). The following limitations/biases and considerations should be noted when interpreting the trial results:

- The single-group, non-comparative design of the trial makes attributing efficacy and safety events to blinatumomab difficult since all patients received the same treatment. Further, the trial is at risk of biases inherent to observational design (e.g., patient selection/ascertainment bias) that can affect a trial's internal validity.
- Although not a limitation, it should be noted that the estimation of the trial's sample size (and thus power) was based on rejecting the null hypothesis that a CR within the first two treatment cycles was ≤10% versus the alternate hypothesis of 27.5%. The trial (phase 2) was deemed a success if nine or more patients out of 40 achieved a CR (22.5%). This success criterion was based on the response rate of clofarabine.
- The trial publication did not provide data on the previous treatment history of patients. These data were requested, but the Submitter provided raw data that precluded a meaningful assessment of this important variable (and comparison to data provided by the Submitter on historical controls, refer to Section 7). Without knowledge of the prior treatments received among patients, the ability to interpret the efficacy results and the generalizability of those results is made difficult.
- The trial publication suffers from incomplete reporting of outcomes, as pooled analyses, which were exploratory analyses of the trial, were the

focus of the trial publication and the analysis of key secondary outcomes (phase 2) were omitted.

- The results of patient subgroup analyses should be interpreted with caution since they were exploratory and therefore unadjusted for multiple testing (i.e., type 1 error), and many subgroups included small numbers of patients, which calls into question the validity and precision of the estimates obtained.
- The trial did not collect data on health-related QOL; thus the direction and degree to which blinatumomab affects patient-reported QOL parameters in pediatric/adolescent patients with relapsed/refractory B-cell precursor ALL are unknown.

Table 6. Baseline patient characteristics in trial MT103-205[1] evaluating blinatumomab in pediatric/adolescent patients with refractory or relapsed B-cell precursor ALL.

Demographic and baseline characteristics	All patients in phase 2	All patients in phase 1 and 2 at recommended dose*
	N (%), unless otherwise specified	
No. of enrolled patients	***44***	***70***
Age, median (range) in years	10.5 (<1-17)	8 (<1-17)
Age group, years <2 2-6 7-17	 2 (5) 11 (25) 31 (71)	 10 (14) 20 (29) 40 (57)
Sex Male Female	 32 (73) 12 (27)	 47 (67) 23 (33)
Geographic region European Union United States	 31 (71) 13 (30)	 48 (69) 22 (31)
Ethnicity/Race[a] White Asian Black Other Unknown	 33 (75)[2] 0 0 5 (11)[2] 6 (14)[2]	 55 (87)[13] NR NR 8 (13)[13] NR
Genetic abnormalities MLL total MLL-AF4.t (4;11) Other MLL BCR-ABL Hypodiploidy Constitutional trisomy 21	 2 (5) 2 (5) 0 1 (2) 3 (7) 1 (2)	 10 (14)[b] 8 (11) 2 (3) 2 (3) 4 (9) 2 (3)
Previous alloHSCT Yes No	 25 (57) 19 (43)	 40 (57) 30 (43)
Previous relapses 0 1 2 ≥3	 0 22 (50) 19 (43) 3 (7)	 2 (3) 31 (44) 29 (41) 8 (11)
Refractory disease	26 (59)	39 (56)
Time between last relapse and first blinatumomab infusion, median (range) in months	1.9 (0.2-13.7)	2.9 (0.4-49.8)
Bone marrow blast count per central laboratory <50 ≥50	 12 (27) 32 (73)	 18 (26) 52 (74)
Abbreviations: alloHSCT - allogeneic hematopoietic stem cell transplant; BCR-ABL - breakpoint cluster region-Abelson murine leukemia viral oncogene homolog 1 gene; MLL - mixed-lineage leukemia gene; NR - not reported.		
Notes:		

* All patients treated at stepwise dosage of 5/15 µg/m^2/d in phase 1 or 2.
[a] Race was not recorded for any patient in France and two other patients.
[b] Eight patients with MLL translocations were <2 years old: six had MLL with the fusion partner AF4.t(4;11); two had other MLL abnormalities.

Table 7. Patient disposition[a] in trial MT103-205[1] evaluating blinatumomab in pediatric/adolescent patients with refractory or relapsed B-cell precursor ALL.

Patient disposition	All patients in phase 2	All patients in phase 1 and 2 at recommended dose*
	Number of patients, n (%)	
Screened	59[b]	113
Enrolled/treated	44	70
Included in primary analysis	44	70
Treatment cycles received[c]		
1	41 (93)	67 (96)
2	11 (25)	22 (31)
3	5 (11)	7 (10)
4	3 (7)	3 (4)
5	3 (7)	3 (4)
Discontinuing treatment	27 (61)	49 (70)[2]
Death	25 (57)[2]	43 (61)[2]
Withdrawal by subject	2 (5)	4 (6)[2]
Completed end of follow-up period	0	0
Lost to follow-up	0	1 (1)[2]
Physician decision	0	1 (1)[2]
Protocol violation	0	0
Study Ongoing	17 (39)[2]	21 (30)[2]

Notes:
* All patients treated at stepwise dosage of 5/15 µg/m^2/d in phase 1 or 2.
[a] Patient disposition at the time of primary analysis.
[b] Fifteen patients were deemed ineligible: bone marrow blasts did not meet inclusion criteria (n=5), CNS involvement (n=4), comorbidities (n=3, infection; n=1, bleeding), administrative (n=1, Sponsor requested more recent sample to analyze % blasts in bone marrow, n=1, scheduling difficulties).
[c] One patient received retreatment.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

A summary of the efficacy results from the MT103-205 trial is provided in Table 8[1]. As previously mentioned, not all secondary outcomes were reported separately for the patients in the phase 2 portion of the trial; thus pCODR requested the Submitter provide these data (i.e., time-to-hematological relapse, RFS, OS). The primary efficacy analysis was performed on January, 12, 2015 and the study was completed on May 24, 2016 after a follow-up period of two years. The estimates summarized below are from the primary analysis unless otherwise specified.

Efficacy Outcomes

Complete Remission (Hematologic Response)

Phase 2

At primary analysis, 32% of patients (n=14/44) achieved a CR within the first two treatment cycles (12 weeks). Among these patients, 14% (n=6) achieved a CR with full recovery of PBC, while 11% (n=5) achieved incomplete PBC recovery, and 7% (n=3) had neither full nor incomplete PBC recovery. MRD response and complete MRD response were both obtained in 57% of patients (n=8/14). For CR rates by baseline blast percentage, refer to Table 8.

Pool Analysis (Phase 1 and 2)

Among the 70 pooled analysis patients, 39% (n=27/70) achieved a CR within the first two treatment cycles; with 17% (n=12) achieving a CR with full PBC recovery, 16% (n=11) with incomplete PBC recovery, and 6% (n=4) with neither full nor incomplete PBC recovery. MRD response and complete MRD response were both obtained in 52% of patients (n=14/27). For CR rates by baseline blast percentage, refer to Table 8.

Hematological response was examined for pre-specified subgroups of patients including geographic region, age (<2, age 2-6, 7-17), previous HSCT, number of previous relapses, refractory disease and bone marrow blast percentage at baseline. The CR estimates obtained for some patient groups, which are summarized in Table 9, should be interpreted with caution as sample sizes were small and resulted in very wide confidence intervals (i.e., low precision).

Ability to Proceed to HSCT

Phase 2

All patients who achieved a CR were eligible to proceed to HSCT. Thirteen patients (30%; n=13/44)) received a HSCT, and of these patients, five (11%) were in a blinatumomab-induced CR and two (5%) were in a CR after only receiving blinatumomab. The 100-day post-HSCT mortality rate (relative to transplant date) was not estimable due to small sample size. There were also eight non-responders (18%) who received subsequent treatment and HSCT.

Pooled Analysis (Phase 1 and 2)

In the pooled analysis, 24 responders (34%; n=24/70) received an HSCT, and of these patients, 13 (19%) were in a blinatumomab-induced CR and eight were in CR after receiving blinatumomab only (11%). The 100-day mortality rate among these patients was 25% (95% CI, 7-69%). Considering non-responders, there were 11 (16%) who received subsequent treatment and HSCT.

Time-to-Hematological Relapse (Duration of Response)

Time-to-hematological relapse was assessed in patients achieving a CR and was measured from the time CR was achieved until first documented relapse or death due to disease progression.

Phase 2

The median follow-up time of all patients with a CR (n=14) was 11.5 months and median time-to-hematological relapse was 3.4 months (95% CI, 1.7-not estimable).[2] Among the 14 responders, four were still in remission (29%), eight relapsed (57%), and two died; one from disease progression (7%) and another from an unspecified cause (7%).[2]

Pooled Analysis (Phase 1 and 2)

The median follow-up time of all pooled patients with a CR (n=27) was 11.5 months and median time-to-hematological relapse was 5.2 months (95% CI, 2.3-16.4). Among the 27 responders, seven were still in remission (26%), 13 relapsed (48%), and seven died; four due to disease progression (15%) and three from other unspecified causes (11%).[2]

Relapse-free Survival

Relapse-free survival was assessed in all patients, and was measured from the time of CR until relapse or death due to any cause without relapse (patients who did not achieve a CR were considered having an event on day one of the analysis).

Phase 2

After a median follow-up time of 11.5 months, the median RFS was 3.4 months (95% CI, 1.7-13.9) among the 14 patients achieving a CR; four were in remission (29%), eight relapsed (57%), and two died without relapse (14%).[2]

Pooled Analysis (Phase 1 and 2)

At the completion of the trial, median follow-up time of all pooled patients achieving a CR (n=27) was 23.1 months, and median RFS was 4.4 months (95% CI, 2.3-7.6). At six months, the RFS rate was 42%.

Overall Survival

Phase 2

The median follow-up time of all patients (n=44) was 11.6 months,[13] at which time median survival was 8.2 months (95% CI, 4.0-14.6).

Pooled Analyses (Phase 1 and 2)

At the completion of the trial, the median OS for all 70 pooled patients was 7.5 months (95% CI, 4.0-11.8) after a median follow-up period of 23.8 months.

Harms Outcomes

Adverse Events

Assessment of AEs was carried out on all patients from phase 1 and 2 (n=70) who received any infusion of blinatumomab at the recommended dose of 5/15 $\mu g/m^2$/day (Table 10). The data cut-off date for the safety analysis was January 12, 2015, and captured AEs during the treatment period and up to 30 days after the last infusion of blinatumomab or before HSCT or the start of chemotherapy.

The most common AEs due to any cause were pyrexia (80%), anemia (41%), nausea (33%), and headache (30%). The most frequent grade ≥3 AEs were primarily cytopenias, and included anemia (36%), thrombocytopenia (21%), neutropenia (17%), and febrile neutropenia (17%). Liver function parameters, including ALT (n=13), AST (n=10) and blood bilirubin (n=4), were elevated in 39% (n=27) of patients. It was reported that the majority of AEs occurred during the first few days of the first treatment cycle. Six patients (9%) experienced fatal AEs, of which three died post-allogeneic HSCT after blinatumomab-induced remission. These deaths were preceded by multiorgan failure, sepsis, and respiratory failure.

Treatment-emergent AEs (TEAEs)[2] occurred in all patients (all grade, 100%; grade ≥3, 87%) and serious TEAEs occurred in 56% of patients (grade ≥3, 28%) with the most frequent being pyrexia (11%), febrile neutropenia (11%), and neurologic events (7%) that included convulsions, confusional state, atonic seizures and neuralgia. All neurologic events resolved except for the one patient with confusional state, and 13% of these events, primarily tremor and dizziness, were deemed treatment-related. Eight patients (11%) experienced fatal TEAEs; these deaths were preceded by multiorgan failure, sepsis, fungal infection, recurrent leukemia, disease progression, respiratory failure, and thrombocytopenia. TEAEs lead to treatment interruption in 14% (n=10) of patients and discontinuation of study drug in 6% (n=4) of patients; with two discontinuations deemed treatment-related (due to grade 3 and 4 CRS). In 84% of patients TEAEs were judged related to treatment with blinatumomab (54% were grade ≥3). There were no fatal treatment-related TREAs in the trial.

Cytokine-release syndrome of any grade occurred in 8 of the 70 patients (11%). The worst grade observed was grade 3 in 4% (n=3) of patients and grade 4 in 1% (n=1), which lasted a median duration of 6.5 days (95% CI, 5.0-16.0). Treatment was either interrupted (n=2) or permanently discontinued (n=2) in these patients; however, all four achieved a CR at the 12-week response assessment.

Table 8. Efficacy outcomes in trial MT103-205[1] evaluating blinatumomab in pediatric/adolescent patients with refractory or relapsed B-cell precursor ALL.

Efficacy Outcomes[a]	All patients in phase 2			All patients in phase 1 and 2 at recommended dose*		
	No. Patients	%	95% CI	No. Patients	%	95% CI
Primary CR within first two treatment cycles[b]	14	32	19-48	27	39	27-51
M1 marrow, full recovery of PBC[c]	6	14	5-27	12	17	9-28
M1 marrow, incomplete recovery of PBC[d]	5	11	4-25	11	16	8-26
M1 marrow, neither full nor incomplete recovery of PBC	3	7	1-19	4	6	2-14
No response (did not achieve a CR):	30	68	NR	43	61	NR
Partial remission[e]	3	7	NR	4	6	NR
Blast-free hypoplastic or aplastic bone marrow	0	0	NR	2	3	NR
Progressive disease[f]	8	18	NR	10	14	NR
No response	14	32	NR	21	30	NR
No response assessment[g]	5	11	NR	6	9	NR
CR within first two treatment cycles by baseline bone marrow blast count						
<50% blasts at baseline	5/12	42	15-72	10/18	56	31-79
≥50% blasts at baseline	9/32	28	14-47	17/52	33	20-47
Secondary Ability to proceed to HSCT						
Patients who received alloHSCT	13	30	NR	24	34	NR
Patients in blinatumomab-induced CR	5	11	NR	13	19	NR
Patients in CR who received only blinatumomab	2	5	NR	8	11	NR
Non-responders who received subsequent treatment	8	18	NR	11	16	NR
Relapse or death after CR[h]	10/14	71	NR	7/27	26	NR
Median time-to-hematological relapse in months (includes only responders)	Median	95% CI		Median	95% CI	
	3.4[2]	1.7-NE[2]		5.2[2]	2.3-16.4[2]	
Relapse-free survival (includes only responders)	3.4[2]	1.7-13.9[2]		4.4	2.3-7.6[k]	
Overall survival	8.2	4.0-14.6[k]		7.5	4.0-11.8[k]	
Exploratory MRD response in patients who achieved CR within first two treatment cycles						
MRD response[i]	8/14	57	29-82	14/27	52	32-71
Complete MRD response[j]	8/14	57	29-82	14/27	52	32-71
M1 marrow, full recovery of PBC[c]	4/6	67	NR	7/12	58	NR
M1 marrow, incomplete recovery of PBC[d]	3/5	60	NR	5/11	46	NR
M1 marrow, neither full nor incomplete recovery of PBC)	1/3	33	NR	2/4	50	NR
No MRD response	6	43	NR	12	44	NR

Abbreviations: alloHSCT - allogeneic hematopoietic stem cell transplant; CI - confidence interval; CR - complete remission; HSCT - hematopoietic stem cell transplant; MRD - minimal residual disease; NR - not reported; PBC - peripheral blood count.

Notes:
* All patients treated at stepwise dosage of 5/15 µg/m^2/d in phase 1 or 2.
[a] Based on the primary analysis on January 12, 2015.
[b] CR defined as no evidence of circulating blasts or extra-medullary disease, and M1 bone marrow (<5% blasts in bone marrow).

[c] M1 marrow (<5% blasts in bone marrow) with platelets >100x10^9/L and absolute neutrophil count >1.0x10^9/L.
[d] M1 marrow (<5% blasts in bone marrow) with platelets >50x10^9/L and absolute neutrophil count ≤100x10^9/L, and platelets ≤100x10^9/L or absolute neutrophil count ≤1.0x10^9/L.
[e] Complete disappearance of circulating blasts and achievement of M2 marrow status (≥5% <25% blast cells) and appearance of normal progenitor cells.
[f] An increase of at least 25%, or an absolute increase of at least 5000 cells/µl (whichever is greater) in the number of circulating leukemia cells, development of extramedullary disease, or other laboratory or clinical evidence of progressive disease.
[g] Patients died (n=5) or withdrew consent (n=1) prior to first response assessment.
[h] Relapse during the efficacy follow-up period with no chemotherapy or alloHSCT between end of blinatumomab treatment and relapse.
[i] MRD <10^{-4} detectable blasts measured either by PCR or flow cytometry.
[j] No detectable blasts either by PCR or flow cytometry.
[k] Based on analysis at completion of trial (May 24, 2016).

Table 9: Complete remission rates* among patient subgroups (from phase 1 and 2 at recommended dose of blinatumomab) in trial MT103-205.[1]

Patient Subgroup	n/N	CR% (95% CI)
All patients	*27/70*	*39 (27-51)*
Geographic region		
Europe	19/48	40 (26-55)
United States	8/22	36 (17-59)
Age group, years		
<2	6/10	60 (26-88)
2 to 6	8/20	40 (19-64)
7 to 17	13/40	33 (19-49)
Previous HSCT		
No	8/30	27 (12-46)
Yes	19/40	48 (32-64)
Previous relapses		
0	0/2	0 (0-84)
1	10/31	32 (17-51)
2	14/29	48 (29-68)
≥3	3/8	38 (9-76)
Refractory disease		
No	15/31	48 (30-67)
Yes	12/39	31 (17-48)
Bone marrow blasts at baseline		
<50%	10/18	56 (31-79)
≥50%	17/52	33 (20-47)
Abbreviations: CR - complete remission; HSCT - hematopoietic stem-cell transplant.		
*Complete remission rates within two treatment cycles of blinatumomab.		

Table 10. Adverse events in trial MT103-205[1] evaluating blinatumomab in pediatric/adolescent patients with refractory or relapsed B-cell precursor ALL.

Adverse Events, n (%)[a]	All patients in phase 1 and phase 2 at recommended dose (n=70)	
	All grade	Grade ≥3
All-cause AEs		
Any AEs occurring in ≥5% of patients	70 (100)	61 (87)
Pyrexia	56 (80)	10 (14)
Anemia	29 (41)	25 (36)
Nausea	23 (33)	NR
Headache	21 (30)	NR
Hypertension	18 (26)	4 (6)
Vomiting	17 (24)	NR
Hypokalemia	15 (21)	12 (17)
Thrombocytopenia	15 (21)	15 (21)
Back pain	14 (20)	NR
Cough	14 (20)	NR
Febrile neutropenia	14 (20)	12 (17)
Abdominal pain	13 (19)	NR
Alanine aminotransferase increased	13 (19)	11 (16)
Weight increased	12 (17)	NR
Neutropenia	12 (17)	12 (17)
Aspartate aminotransferase increased	10 (14)	8 (11)
Hypotension	10 (14)	NR
Epistaxis	10 (14)	NR
Platelet count decreased	10 (14)	10 (14)
Hypophosphatemia	10 (14)	NR
Diarrhea	9 (13)	NR
Leukopenia	9 (13)	7 (10)
Neutrophil count decreased	9 (13)	9 (13)
Pain in extremity	8 (11)	NR
Cytokine release syndrome	8 (11)	4 (6)
White blood cell count decreased	8 (11)	7 (10)
Hypocalcemia	8 (11)	NR
Bone pain	7 (10)	NR
Blood lactate dehydrogenase increased	7 (10)	NR
Rhinitis	7 (10)	NR
Pain	6 (9)	NR
Fibrin D dimer increased	6 (9)	NR
Constipation	6 (9)	NR
Hyperglycemia	6 (9)	NR
Hypomagnesemia	6 (9)	NR
Fatigue	5 (7)	NR
Hyponatremia	5 (7)	NR
Edema peripheral	5 (7)	NR
Sinus tachycardia	5 (7)	NR
Stomatitis	5 (7)	NR
Blood bilirubin increased	4 (6)	NR
Hypoalbuminemia	4 (6)	NR
Anxiety	4 (6)	NR
Hypoxia	4 (6)	NR
Activated partial thromboplastin time prolonged	4 (6)	NR
Non-cardiac chest pain	4 (6)	NR
Arthralgia	4 (6)	NR
Atelectasis	4 (6)	NR
Muscular weakness	4 (6)	NR
Weight decreased	4 (6)	NR
Neurologic/psychiatric	17 (24)	NR

Adverse Events, n (%)[a]	All patients in phase 1 and phase 2 at recommended dose (n=70)	
	All grade	Grade ≥3
Tremor	4 (6)	NR
Dizziness	3 (4)	NR
Somnolence	3 (4)	2 (3)*
Convulsion	2 (3)	NR
Paresthesia	2 (3)	NR
Encephalopathy	1 (1)	NR
Neuralgia	1 (1)	1 (1)*
Ataxia	1 (1)	NR
Atonic seizure	1 (1)	NR
Cerebrospinal fluid leakage	1 (1)	NR
Depressed level of consciousness	1 (1)	NR
Dysgeusia	1 (1)	NR
Hypoesthesia	1 (1)	NR
Nystagmus	1 (1)	NR
Syncope	1 (1)	NR
Confusional state	1 (1)	NR
Mental disorder	1 (1)	NR
Fatal AEs	6 (7)[b]	NR
Multiorgan failure	2 (3)[c]	NR
Sepsis	1 (1)[c]	NR
Fungal infection	1 (1)	NR
Respiratory failure	1 (1)[c]	NR
Thrombocytopenia	1 (1)	NR
Treatment-emergent AEs (TEAEs)[2]		
Any TEAEs	70 (100)	61 (87)
TESAEs	39 (56)	28 (40)
Pyrexia	8 (11)	NR
Febrile neutropenia	8 (11)	NR
Cytokine release syndrome	4 (6)	NR
Respiratory failure	2 (3)	NR
Neurologic	5 (7)	NR
Convulsion	2 (3)	NR
Confusional state	1 (1)	NR
Atonic seizures	1 (1)	NR
Neuralgia	1 (1)	NR
Fatal TEAEs	8 (11)	NR
Multiorgan failure	2 (3)	NR
Sepsis	1 (1)	NR
Fungal infection	1 (1)	NR
Recurrent leukemia	1 (1)	NR
Death	1 (1)	NR
Respiratory failure	1 (1)	NR
Thrombocytopenia	1 (1)	NR
TEAEs leading to treatment interruption	10 (14)	NR
TEAEs leading to discontinuation of study drug	4 (6)	NR
TEAEs leading to death	8 (11)	NR
Treatment-related TEAEs[2]		
Treatment-related TEAEs	59 (84)	38 (54)
Treatment-related TESAEs	15 (21)	NR
Treatment-related TESAEs leading to discontinuation of study drug	2 (3)	NR
Treatment-related TESAEs leading to death	0	NR

Abbreviations: AEs-adverse events; TEAEs-treatment-emergent adverse events; TESAEs-treatment-emergent serious adverse events.

Adverse Events, n (%)[a]	All patients in phase 1 and phase 2 at recommended dose (n=70)	
	All grade	Grade ≥3
Notes: *Grade 3 only. [a] AEs assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03, regardless of causality that occurred during the treatment period and until 30 days after last treatment or before allogeneic HSCT or start of chemotherapy. AEs were deemed related or unrelated to treatment with blinatumomab by investigators. [b] Does not include two deaths caused by disease progression, including one patient who died as a result of recurrent leukemia. These deaths were reported as AEs by investigators. [c] Patient died after allogeneic HSCT after blinatumomab-induced CR (only one of the patients with multiorgan failure).		

6.4 Ongoing Trials

No ongoing trials were identified.

7 SUPPLEMENTAL QUESTIONS

The following supplemental question was identified during development of the review protocol as relevant to the pCODR review of blinatumomab for pediatric/adolescent patients with Philadelphia chromosome-negative (Ph-) relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL).

- Critical appraisal of historical comparator study 20140228: a retrospective cohort study of reinduction treatment outcome among pediatric patients with relapsed or refractory B-cell precursor ALL

Topics considered in this section are provided as supporting information. The information has not been systematically reviewed.

7.1 Critical Appraisal of Historical Comparator Study 20140228

7.1.1 Objective

The pivotal clinical trial (MT103-205)[1] included in the pCODR systematic review to assess the efficacy and safety of blinatumomab in the specified population (above) was a non-randomized trial. In order to provide a frame of reference for the efficacy of blinatumomab, the Submitter provided pCODR with the results of a historical comparator study[2] that they conducted to estimate the efficacy of contemporary standard of care (SOC) treatments, including chemotherapy, targeted and other salvage therapies, in pediatric patients with relapsed/refractory B-cell precursor ALL who relapsed after HSCT, were in second or later relapse, or had refractory disease. The primary objective of study 20140228 was to estimate complete remission (CR) in the historical cohort, and to develop a weighted CR to serve as an external comparator to the CR estimate obtained in the blinatumomab trial. Secondary objectives included estimating overall survival (OS), relapse-free survival (RFS), event-free survival (EFS), and the receipt of hematopoietic stem cell transplantation (HSCT), as well as weighted estimates of these outcomes to compare to the blinatumomab trial.

7.1.2 Methodology

By design, study 20140228 was a retrospective cohort study of pediatric patients who were treated between 2005 and 2013 at clinical sites in the US, Canada, and Australia belonging to the Therapeutic Advances in Childhood Leukemia and Lymphoma (TACL) Consortium. Fourteen of 36 TACL sites participated in the study. Initially, eligible patients included patients with relapsed/refractory B-precursor ALL who experienced a qualifying treatment failure between 2005 and 2013 and who were ≤21 years at the time of qualifying treatment failure. A qualifying treatment failure was any treatment failure except for first relapse without prior HSCT. Additional inclusion criteria were later applied to more closely align the study population to patients enrolled in the MT103-205 trial, which included age <18 years, bone marrow blasts >25% before salvage therapy, no CNS involvement, and no previous treatment with blinatumomab.

Patient data were collected from three study periods, including (1) from initial diagnosis of ALL to the time of second relapse after chemotherapy, relapse after HSCT or refractory disease, (2) at the time of relapsed/refractory disease, and 3) from relapsed/refractory disease to death or end of follow-up (at least to December 31, 2014, to allow at least one year of follow-up after treatment). Data were collected on demographic and clinical characteristics, and initial and subsequent treatments. The study used the identical definition of CR that was used in the blinatumomab trial. For time-to-event outcomes, follow-up time was calculated from the date of last salvage therapy, or date of last relapse to death, or last follow-up date.

After an initial review of the historical study data, it was clear that the distributions of important baseline characteristics of patients were different between trial 20140228 and MT103-

205. To account for this, the primary analysis of the comparator study initially was to be weighted by disease stage (i.e., previous treatment history), such that outcome estimates were weighted to the distributions of these variables in the MT103-205 trial. However, after further review of the collected data and a discussion with clinical experts, additional important prognostic variables were added (i.e., bone marrow blast percentage prior to treatment, prior HSCT, and time from prior chemotherapy or HSCT). Notable differences in these variables at baseline were also observed; the MT103-205 trial had higher proportions of patients in the strata of these variables associated with poorer prognosis. To adjust for these differences additional ad-hoc weighted analyses were performed. For both analyses (primary and ad-hoc), outcome estimates were obtained for first qualifying salvage treatment (considered to provide the most conservative estimates of efficacy) and last qualifying salvage treatment (considered the most appropriate analysis since it most closely aligned with patients in the MT103-205 trial).

The weighted analysis approach described above is limited by the number of variables that can be examined (due to small sample size in some patient subgroups), and therefore is at risk of confounding since not all important variables (covariates) can be controlled for simultaneously. To overcome this issue, a propensity score analysis method was performed. The Submitter did not initially provide the results of this analysis; however, upon receipt and review, the propensity score analysis conducted actually includes data from a second historical study conducted in Europe (study 20120229). Outcome estimates for study 20140228 were separately reported, based on propensity score analyses performed by region; the results of these analyses, and not the combined analysis involving both comparator studies, are summarized below.

In brief, propensity score analysis aims to achieve balance between treatment groups (i.e., SOC and blinatumomab) with respect to important known (measured) covariates. In a randomized trial, each patient has an equal probability of being assigned to a treatment group; however, in an observational study, patients have variable probabilities (or propensity) of receiving treatment. The propensity score method estimates the probability (value) of receiving treatment for each patient in a group using logistic regression models that include measured covariates, which allows for statistical inferences to be made. The goal is to fit the model as closely as possible to the data with as many potential cofounding covariates as possible, in order to balance them between groups. Although propensity score methods mimic randomization, unlike randomization, they do not control for unmeasured or unknown covariates.[21]

For study 20140228, propensity scores for each patient were estimated using [redacted]. (*Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until August 1, 2018 or until notification by manufacturer that it can be publicly disclosed, whichever is earlier*.)

7.1.3 Findings

At the time of primary analysis ([redacted]), a total of 121 patients met all the eligibility requirements and comprised the primary analysis set.[23] Table 12 provides a summary of the baseline characteristics of patients in historical comparator study 20140228, including a breakdown of prognostic variables by first and last qualifying salvage treatment. Data on the type and timing of the previous SOC treatments received by patients were not reported in documents provided by the Submitter (clinical summary and clinical study report), and therefore were requested. The data received indicated [redacted].[2] (*Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until August 1, 2018 or until notification by manufacturer that it can be publicly disclosed, whichever is earlier*.)

Not all efficacy outcomes could be assessed due to missing data (i.e., [redacted]). *Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until August 1, 2018 or until notification by manufacturer that it can be publicly disclosed, whichever is earlier*.) Data were available for the majority of patients for CR (n=[redacted] and n=[redacted], for first and last salvage, respectively) and for all patients for OS. The results of the primary and ad-hoc weighted analyses are summarized in Table 13. The primary analysis (weighted for disease stage) obtained a weighted CR of 30% (95% CI, 20-39%)[23] and a weighted median OS of [redacted] months ([redacted]) for last qualifying salvage. The ad-hoc analysis (weighted for prior HSCT, baseline bone marrow blasts, and time from prior chemotherapy or HSCT, but not disease stage) obtained a weighted CR of [redacted] ([redacted]) and a weighted median OS of [redacted] months ([redacted]) for last qualifying salvage. *Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until August 1, 2018 or until notification by manufacturer that it can be publicly disclosed, whichever is earlier*.) For both analyses, weighted estimates were also calculated for CR with full and incomplete peripheral blood count recovery (refer to Table 13).

For the propensity score analysis, it was reported that application of [redacted]. *Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until August 1, 2018 or until notification by manufacturer that it can be publicly disclosed, whichever is earlier*.)

7.1.4 Limitations

Overall, the historical comparator study analysis and its accompanying propensity analysis suffer from limitations that call into question the validity of findings. Specifically:

Historical Comparator Study Weighted Analysis

- While there were some clear differences in the distribution of important prognostic variables between first and last qualifying salvage (the latter with higher proportions of patients with relapse after HSCT, >2 treatment attempts, and <6 months since prior

chemotherapy or HSCT to salvage treatment), the proportions of these patients with these characteristics were still lower compared to the blinatumomab trial, which included substantially more patients with disease burden and refractory disease. Weighting the estimates obtained by the proportions of these patients in the MT103-205 trial addresses this issue; however, the overall usefulness of the weighted estimates is still questionable, since they are likely confounded, having only been adjusted for the influence of a few and not all important prognostic variables. Further, the small numbers of patients in some patient subgroups precluded obtaining efficacy estimates or resulted in uninterpretable estimates.

- Data on the performance status of patients were not available, therefore it is not clear what differences there may have been in performance status between the two studies and the impact this had on the results obtained.
- Data were provided by the Submitter on the types of previous treatments received by patients, and as expected, indicated significant heterogeneity with respect to the number of treatments, the general category of treatments, treatments within a category, and the combinations of specific chemotherapies used. The submitter said a formal test of heterogeneity could not be performed, nor could a treatment history indicator be constructed given the complexity of heterogeneity. Therefore, treatment history is largely uncontrolled for in analyses. Further, issues of generalizability are also a potential concern, since the majority of patients were treated with clofarabine-based regimens; a chemotherapy not commonly used in Canada.
- The clinical study report provided by the Submitter indicates that approximately [redacted] patients were required to achieve reasonably precise estimates of CR. With a total of 121 patients, it appears the study likely suffers from low power. *Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until August 1, 2018 or until notification by manufacturer that it can be publicly disclosed, whichever is earlier*.)
- Missing data precluded the analysis of other important outcomes, including RFS, EFS, and receipt of HSCT.
- The historical comparator study has not been published, and therefore has not undergone peer-review.

Propensity Score Analysis

- A general limitation of propensity score analysis is that any unknown or unmeasured confounders are not accounted for in analyses.
- Similar to the weighted analysis, the propensity score analysis also did not include data on [redacted]. *Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until August 1, 2018 or until notification by manufacturer that it can be publicly disclosed, whichever is earlier*.) Therefore, these factors were not accounted for as covariates in developing the propensity scores of patients in the analysis. Omitting these variables reduces the effectiveness of the propensity scoring method.

[redacted]The actual propensity scores of patients [redacted]

[redacted]. (*Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until August 1, 2018 or until notification by manufacturer that it can be publicly disclosed, whichever is earlier*.) It is unclear, however, whether the balance assessment also holds true for the separate analysis of the 20140228 historical comparator trial.

- It is unclear why OS was selected as the outcome for the primary analysis versus CR, when both the weighted analysis in the historical comparator study and the blinatumomab trial used CR in primary analyses.
- There is no mention of how missing data were handled in the propensity score analysis. Missing data, if handled incorrectly, can substantially reduce the size of the study sample.

7.1.5 Summary

In order to provide a frame of reference for the efficacy of blinatumomab, the Submitter provided pCODR with the results of a historical comparator study (20140228), which aimed to estimate the efficacy of standard of care treatments (e.g., chemotherapy, targeted therapy) in pediatric patients with relapsed/refractory B-cell precursor ALL. Its objective was to estimate complete remission (CR) in the historical cohort, and to develop a weighted CR to serve as an external comparator to the CR estimate obtained in the blinatumomab trial. Secondary objectives included estimating overall survival (OS), relapse-free survival (RFS), event-free survival (EFS), and the receipt of hematopoietic stem cell transplantation (HSCT), as well as weighted estimates of these outcomes to compare to the blinatumomab trial. The study included patients who experienced a qualifying treatment failure between 2005 and 2013 and were treated at clinical sites in the US, Canada, and Australia belonging to the Therapeutic Advances in Childhood Leukemia and Lymphoma (TACL) Consortium. Eligibility criteria and outcome definitions closely aligned with the MT103-205 trial; however, there were significant differences in the distributions of important baseline characteristics between the studies, with the MT103-205 trial having higher proportions of patients with poorer prognosis. To account for these differences, weighted analyses were performed with outcome estimates weighted to the distributions in the MT103-205 trial for disease stage (primary analysis), and bone marrow blast percentage prior to treatment, prior HSCT, and time from prior chemotherapy or HSCT (ad hoc analyses). A propensity analysis was also performed to control for multiple variables simultaneously. Efficacy estimates were obtained for first and last qualifying salvage, with the latter considered the most appropriate analysis since it most closely resembled patients in the MT103-205 trial.

A total of 121 patients comprised the primary analysis set. Not all efficacy outcomes (i.e., [redacted]) could be assessed due to missing data. Data were available for the majority of patients for CR (n=[redacted] and n=[redacted], for first and last salvage, respectively) and for all patients for OS. *Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until August 1, 2018 or until notification by manufacturer that it can be publicly disclosed, whichever is earlier*.) The primary analysis (weighted for disease stage) obtained a weighted CR of 30% (95% CI, 20-39%) and a weighted median OS of [redacted] months ([redacted]) for last qualifying salvage. The ad-hoc analysis (weighted for prior HSCT, baseline bone marrow blasts, and time from prior chemotherapy or

HSCT, but not disease stage) obtained a weighted CR of [redacted] ([redacted]) and a weighted median OS of [redacted] months ([redacted]) for last qualifying salvage. For the propensity score analysis, the primary analysis of OS [redacted]. (*Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until* ***August*** *1, 2018 or until notification by manufacturer that it can be publicly disclosed, whichever is earlier*.) Limitations with these analyses raise concerns about its usefulness and validity. Specifically, the overall usefulness of the estimates obtained in the weighted analyses is questionable since they are likely confounded having only been adjusted for the influence of a few and not all important variables. Further, the [redacted] were not controlled for in any of the analyses performed, and therefore their influence on the results obtained is unknown. There was incomplete reporting of the methods used for the propensity score analysis making it difficult to judge the utility and validity of the results. The historical study also likely suffers from low power since the number of included patients was much lower than the required sample size (n=[redacted]). (*Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until August 1, 2018 or until notification by manufacturer that it can be publicly disclosed, whichever is earlier*.) For a comprehensive review of the study and its limitations, refer to Section 7.1.

Table 12: Baseline characteristics of patients in historical comparator study 20140228.[2]

Demographic and baseline characteristics	Historical Comparator Study Study 20140228 n (%)	
No. of patients	***121***	
Age, median (range) in years	[redacted]	
Age group, years <1 1-6 7-17		
Sex Male Female		
Ethnicity/Race[a] White Other Unknown		
Qualifying Treatment Salvage	***First***	***Last***
Disease stage at qualifying salvage Without prior HSCT and ≥2 relapses Without prior HSCT and refractory disease Relapse after HSCT	[redacted]	
Number of prior treatment attempts 1 2 >2		
Bone marrow blast count per central laboratory <50 ≥50 Missing		
Response to initial front-line attempt Complete remission Disease refractory		
Time from prior chemotherapy or HSCT (whichever more recent) to date of qualifying salvage chemotherapy 0 to <6 months ≥6 months		

Abbreviations: HSCT -hematopoietic stem cell transplant.

(Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until August 1, 2018 or until notification by manufacturer that it can be publicly disclosed, whichever is earlier.)

Table 13: Strata-specific and combined weighted estimates of complete remission and overall survival by qualifying salvage treatment in historical comparator study 20140228.[2]

Outcome	n/N	Stratum % observed	Estimate (95% CI)	Stratum % observed in MT103-205
Primary analysis adjusted for disease stage (previous lines of treatment)				
*Using first qualifying salvage (n=[redacted])**			CR proportion	
CR without prior HSCT and ≥2 relapses without prior HSCT and refractory relapse after HSCT	[redacted]			
Combined weighted estimate:				
*Using last qualifying salvage (n=[redacted])**				
CR without prior HSCT and ≥2 relapses without prior HSCT and refractory relapse after HSCT	[redacted]			
Combined weighted estimate:				
*Using first qualifying salvage (n=[redacted])**				
CR with full PBC recovery without prior HSCT and ≥2 relapses without prior HSCT and refractory relapse after HSCT	[redacted]			
Combined weighted estimate:				
*Using last qualifying salvage (n=[redacted])**				
CR with full PBC recovery without prior HSCT and ≥2 relapses without prior HSCT and refractory relapse after HSCT	[redacted]			
Combined weighted estimate:				
*Using first qualifying salvage (n=[redacted])**				
CR with incomplete PBC recovery without prior HSCT and ≥2 relapses without prior HSCT and refractory relapse after HSCT	[redacted]			
Combined weighted estimate:				
*Using last qualifying salvage (n=[redacted])**				
CR with incomplete PBC recovery without prior HSCT and ≥2 relapses without prior HSCT and refractory relapse after HSCT	[redacted]			
Combined weighted estimate:				
Using first qualifying salvage (n=[redacted])	Event/N		Median OS	
Median OS without prior HSCT and ≥2 relapses without prior HSCT and refractory relapse after HSCT	[redacted]			
Combined weighted estimate:				
Using last qualifying salvage (n=[redacted])				
Median OS without prior HSCT and ≥2 relapses without prior HSCT and refractory relapse after HSCT	[redacted]			
Combined weighted estimate:				
Ad-hoc analyses adjusted for prior HSCT, baseline bone marrow blast percentage, and time from prior chemotherapy or HSCT[a]				
*Using first qualifying salvage(n=[redacted])**			CR proportion	
CR No prior HSCT, <50% blasts, <6 months	[redacted]			

Outcome	n/N	Stratum % observed	Estimate (95% CI)	Stratum % observed in MT103-205
No prior HSCT, <50% blasts, ≥6 months	[redacted]			
No prior HSCT, ≥50% blasts, <6 months				
No prior HSCT, ≥50% blasts, ≥6 months				
Prior HSCT, <50% blasts, <6 months				
Prior HSCT, <50% blasts, ≥6 months				
Prior HSCT, ≥50% blasts, <6 months				
Prior HSCT, ≥50% blasts, ≥6 months				
Combined weighted estimate:				
*Using last qualifying salvage (n=[redacted])**				
CR	[redacted]			
No prior HSCT, <50% blasts, <6 months				
No prior HSCT, <50% blasts, ≥6 months				
No prior HSCT, ≥50% blasts, <6 months				
No prior HSCT, ≥50% blasts, ≥6 months				
Prior HSCT, <50% blasts, <6 months				
Prior HSCT, <50% blasts, ≥6 months				
Prior HSCT, ≥50% blasts, <6 months				
Prior HSCT, ≥50% blasts, ≥6 months				
Combined weighted estimate:				
*Using first qualifying salvage(n=[redacted])**	Event/N		Median OS	
Median OS	[redacted]			
No prior HSCT, <50% blasts, <6 months				
No prior HSCT, <50% blasts, ≥6 months				
No prior HSCT, ≥50% blasts, <6 months				
No prior HSCT, ≥50% blasts, ≥6 months				
Prior HSCT, <50% blasts, <6 months				
Prior HSCT, <50% blasts, ≥6 months				
Prior HSCT, ≥50% blasts, <6 months				
Prior HSCT, ≥50% blasts, ≥6 months				
Combined weighted estimate:				
*Using last qualifying salvage (n=[redacted])**				
Median OS	[redacted]			
No prior HSCT, <50% blasts, <6 months				
No prior HSCT, <50% blasts, ≥6 months				
No prior HSCT, ≥50% blasts, <6 months				
No prior HSCT, ≥50% blasts, ≥6 months				
Prior HSCT, <50% blasts, <6 months				
Prior HSCT, <50% blasts, ≥6 months				
Prior HSCT, ≥50% blasts, <6 months				
Prior HSCT, ≥50% blasts, ≥6 months				
Combined weighted estimate:				

Abbreviations: CI - confidence interval; HSCT -hematopoietic stem-cell transplant; NE - not estimable; PBC - peripheral blood counts.

Notes:
* Excludes patients who have missing data for these outcomes or who could not be categorized into the three strata based on disease status (without prior HSCT and ≥2 relapses, without prior HSCT and refractory, and relapse after HSCT).
[a] Strata based on prior HSCT (yes versus no), bone marrow blast percentage prior to qualifying salvage (<50% versus ≥50%), and time from most recent chemotherapy or HSCT to date of salvage chemotherapy for qualifying cycle (<6 months versus ≥6 months).

(Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until August 1, 2018 or until notification by manufacturer that it can be publicly disclosed, whichever is earlier.)

8 COMPARISON WITH OTHER LITERATURE

It is not yet known whether standard combination chemotherapy is more effective than blinatumomab in treating relapsed B-cell acute lymphoblastic leukemia (B-ALL). The Clinical Guidance Panel (CGP) identified two relevant ongoing trials investigating blinatumomab in treating pediatric/adolescent patients with relapsed B-cell-ALL. The first trial is the Children's Oncology Group (COG) phase 3 randomized controlled study ALL1331 (NCT02101853).[4] This trial is investigating blinatumomab compared with standard combination chemotherapy in treating patients in first relapse of childhood B-ALL. Patients ages 1 year to 30 years with first relapse of B-ALL are eligible to participate. The primary outcome measure is disease free survival (DFS) of high risk (HR) and intermediate risk (IR) relapse patients from start of block 2 of therapy to event (treatment failure, relapse, second malignancy, death) or last follow-up for those who are event free, assessed up to 10 years, and DFS of low risk (LR) relapse patients (from start of block 3 therapy to the first event or last follow-up for those who are event free, assessed up to 10 years. The secondary outcome measure is overall survival of HR, IR, and LR relapse patients. The trial opened in December 2014, and the estimated primary completion date is April 2018.

The second ongoing trial is a phase 3 randomized controlled trial of blinatumomab compared to standard chemotherapy in pediatric patients with HR first relapse B-ALL (NCT02393859).[22] Children up to 17 years with Philadelphia chromosome negative high-risk first relapse B-ALL are eligible to participate. The primary outcome is event-free survival (EFS) after treatment with blinatumomab when compared to standard of care (SOC) chemotherapy. Overall survival is a key secondary outcome. The trial opened in November 2015 and the estimated primary completion date is January 2020.

Both ongoing trials were not included in the pCODR systematic review because both studies include pediatric patients with B-ALL in the first relapse. The inclusion criteria for the pCODR systematic review is for second or later relapse. While these phase 3 randomized controlled trials of blinatumomab do not meet criteria for the pCODR review, the CGP acknowledge that these trials are expected to answer the role of blinatumomab in the relapse pediatric B-ALL setting more definitely than the current body of evidence.

9 ABOUT THIS DOCUMENT

This Clinical Guidance Report was prepared by the pCODR pediatric Leukemia Clinical Guidance Panel and supported by the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding the clinical evidence available on blinatumomab for pediatric patients with Philadelphia chromosome-negative relapsed or refractory B-cell precursor acute lymphoblastic leukemia. Issues regarding resource implications are beyond the scope of this report and are addressed by the relevant pCODR Economic Guidance Report. Details of the pCODR review process can be found on the CADTH website (www.cadth.ca/pcodr).

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Clinical Guidance Report was handled in accordance with the pCODR Disclosure of Information Guidelines. The manufacturer, as the primary data owner, did not agree to the disclosure of some clinical information which was provided to pERC for their deliberations, and this information has been redacted in this publicly posted Guidance Report.

This Final Clinical Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Clinical Guidance Report supersedes the Initial Clinical Guidance Report. Note that no revision was made in between posting of the Initial and Final Clinical Guidance Reports.

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Clinical Guidance Report was handled in accordance with the pCODR Disclosure of Information Guidelines. There was no non-disclosable information in the Clinical Guidance Report provided to pERC for their deliberations.

APPENDIX A: LITERATURE SEARCH STRATEGY

See Appendix B for more details on literature search methods.

1. Literature search via OVID platform

Database(s): **EBM Reviews - Cochrane Central Register of Controlled Trials** February 2017**, Embase** 1974 to 2017 March 20**, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)** 1946 to Present
Search Strategy:

#	Searches	Results
1	(Blinatumomab* or Blincyto* or AMG103 or AMG-103 or MT-103 or MT103 or MEDI-538 or MEDI538 or 853426-35-4 or 4FR53SIF3A).ti,ab,ot,kf,kw,hw,rn,nm.	1042
2	Precursor Cell Lymphoblastic Leukemia-Lymphoma/	37589
3	exp Precursor B-Cell Lymphoblastic Leukemia-Lymphoma/	45338
4	(acute adj3 (lymphocytic or lymphoid or lymphatic or lymphocyte) adj3 (leukemia* or leukaemia*)).ti,ab,kf,kw.	15415
5	((B-cell or B-cells or B precursor or Pro-B or Pre-B or Burkitt* or B-lineage) adj3 (leukemia* or leukaemia*)).ti,ab,kf,kw.	18985
6	lymphoblast*.ti,ab,kf,kw.	112778
7	2 or 3 or 4 or 5 or 6	155484
8	1 and 7	647
9	8 use pmez	138
10	8 use cctr	9
11	*blinatumomab/	229
12	(Blinatumomab* or Blincyto* or AMG103 or AMG-103 or MT-103 or MT103 or MEDI-538 or MEDI538).ti,ab,kw.	606
13	11 or 12	614

14	exp Acute lymphoblastic leukemia/	69381
15	(acute adj3 (lymphocytic or lymphoid or lymphatic or lymphocyte) adj3 (leukemia* or leukaemia*)).ti,ab,kw.	15393
16	((B-cell or B-cells or B precursor or Pro-B or Pre-B or Burkitt* or B-lineage) adj3 (leukemia* or leukaemia*)).ti,ab,kw.	18952
17	lymphoblast*.ti,ab,kw.	112660
18	14 or 15 or 16 or 17	155518
19	13 and 18	412
20	19 use oemezd	276
21	20 and conference abstract.pt.	121
22	limit 21 to yr="2012 -Current"	102
23	19 not 21	291
24	9 or 10 or 23	302
25	remove duplicates from 24	181
26	22 or 25	283
27	limit 26 to english language	278

2. Literature search via PubMed

A limited PubMed search was performed to capture records not found in MEDLINE.

Search	Query	Items found
#9	Search **#7 AND #8** Filters: **English**	9
#8	Search **publisher[sb]** Filters: **English**	501772
#7	Search **#1 AND (#2 OR #3 OR #4 OR #5)** Filters: **English**	134
#6	Search **#1 AND (#2 OR #3 OR #4 OR #5)**	137

Search	Query	Items found
#5	Search **lymphoblast*[tiab]**	47673
#4	Search **(B-Cell[tiab] OR B-cells[tiab] OR B precursor[tiab] OR Pro-B[tiab] OR Pre-B[tiab] OR Burkitt*[tiab] OR B-lineage[tiab]) AND (leukemia*[tiab] OR leukaemia*[tiab])**	19720
#3	Search **acute[tiab] AND (lymphocytic[tiab] OR lymphoid[tiab] OR lymphatic[tiab] OR lymphocyte[tiab]) AND (leukemia*[tiab] OR leukaemia*[tiab])**	13100
#2	Search **Precursor Cell Lymphoblastic Leukemia-Lymphoma[mh]**	24305
#1	Search **Blinatumomab* OR Blincyto* OR "AMG103" OR "AMG-103" OR "MT-103" OR "MT103" OR "MEDI-538" OR "MEDI538"**	201

3. **Cochrane Central Register of Controlled Trials (Central)**
   Searched via Ovid

4. **Grey Literature search via:**

Clinical trial registries:

U.S. NIH ClinicalTrials.gov
http://www.clinicaltrials.gov/

Canadian Partnership Against Cancer Corporation. Canadian Cancer Trials
http://www.canadiancancertrials.ca/

Search: Blincyto/blinatumomab, acute lymphoblastic leukemia

Select international agencies including:

Food and Drug Administration (FDA):
http://www.fda.gov/

European Medicines Agency (EMA):
http://www.ema.europa.eu/

Search: Blincyto/blinatumomab, acute lymphoblastic leukemia

Conference abstracts:

American Society of Clinical Oncology (ASCO)
http://www.asco.org/

American Society of Hematology
http://www.hematology.org/

Search: Blincyto/blinatumomab, acute lymphoblastic leukemia - last 5 years

APPENDIX B: LITERATURE SEARCH STRATEGY AND DETAILED METHODOLOGY

Literature Search Methods

The literature search was performed by the pCODR Methods Team using the search strategy provided in Appendix A.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946-present) with Epub ahead of print, in-process records & daily updates via Ovid; Embase (1974-2017 March 20) via Ovid; The Cochrane Central Register of Controlled Trials (February 2017) via Ovid; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were blinatumomab, Blincyto and acute lymphoblastic leukemia.

No filters were applied to limit retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English-language documents, but not limited by publication year.

The search is considered up to date as of July 5, 2017.

Grey literature (literature that is not commercially published) was identified by searching the websites of regulatory agencies (Food and Drug Administration and European Medicines Agency), clinical trial registries (U.S. National Institutes of Health – clinicaltrials.gov and Canadian Partnership Against Cancer Corporation - Canadian Cancer Trials), and relevant conference abstracts. Conference abstracts were retrieved through a search of the Embase database limited to the last five years. Abstracts from the American Society of Clinical Oncology (ASCO) and the American Society of Hematology (ASH) were searched manually for conference years not available in Embase. Searches were supplemented by reviewing the bibliographies of key papers and through contacts with the Clinical Guidance Panel. In addition, the manufacturer of the drug was contacted for additional information as required by the pCODR Review Team.

Study Selection

One member of the pCODR Methods Team selected studies for inclusion in the review according to the predetermined protocol. All articles considered potentially relevant were acquired from library sources. Two members of the pCODR Methods Team independently made the final selection of studies to be included in the review and differences were resolved through discussion.

Included and excluded studies (with reasons for exclusion) are identified in section 6.3.1.

Quality Assessment

Assessment of study bias was performed by one member of the pCODR Methods Team with input provided by the Clinical Guidance Panel and other members of the pCODR Review Team. SIGN-50 Checklists were applied as a minimum standard. Additional limitations and sources of bias were identified by the pCODR Review Team.

Data Analysis

No additional data analyses were conducted as part of the pCODR review.

Writing of the Review Report

This report was written by the Methods Team, the Clinical Guidance Panel and the pCODR Secretariat:

- The Methods Team wrote a systematic review of the evidence and summaries of evidence for supplemental questions.
- The pCODR Clinical Guidance Panel wrote a summary of background clinical information and the interpretation of the systematic review. The Panel provided guidance and developed conclusions on the net clinical benefit of the drug.
- The pCODR Secretariat wrote summaries of the input provided by patient advocacy groups, by the Provincial Advisory Group (PAG), and by Registered Clinicians.

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