pCODR EXPERT REVIEW COMMITTEE (pERC)
INITIAL RECOMMENDATION

The CADTH pan-Canadian Oncology Drug Review (pCODR) was established by Canada's provincial and territorial Ministries of Health (with the exception of Quebec) to assess cancer drug therapies and make recommendations to guide drug reimbursement decisions. The pCODR process brings consistency and clarity to the assessment of cancer drugs by looking at clinical evidence, cost-effectiveness, and patient perspectives.

Providing Feedback on This Initial Recommendation
Taking into consideration feedback from eligible stakeholders, the pCODR Expert Review Committee (pERC) will make a Final Recommendation. Feedback must be provided in accordance with *pCODR Procedures*, which are available on the pCODR website. The Final Recommendation will be posted on the pCODR website once available, and will supersede this Initial Recommendation.

Drug:
Blinatumomab (Blincyto)

Submitted Funding Request: For the treatment of pediatric patients with Philadelphia chromosome-negative (Ph-) relapsed or refractory B precursor acute lymphoblastic leukemia (ALL)

Submitted by:
Amgen Canada Inc.

Manufactured by:
Amgen Canada Inc.

Notice of Compliance Date:
April 28, 2017

Initial Recommendation Issued:
August 3, 2017

Approximate per Patient Drug Costs, per Month (28 Days)	**Blinatumomab regimen costs:**
Submitted list price of $2,978.26 per 38.5 µg of lyophilized powder in a single-use vial for reconstitution. Note: Costs are calculated based on patients weighing ≥ 45 kg (fixed dose). Dosage for patients weighing < 45 kg is based on body surface area.	$55,594.20 per 28-day course

pERC RECOMMENDATION

pERC recommends funding blinatumomab (Blincyto) in pediatric patients with Philadelphia chromosome-negative (Ph−) relapsed or refractory B precursor acute lymphoblastic leukemia (ALL) and who are in second or later relapse, who relapsed after allogeneic hematopoietic stem cell transplant (alloHSCT) or who have refractory disease, conditional on cost-effectiveness being improved to an acceptable level. Treatment should be in patients with a good performance status and administered as a four-week continuous infusion followed by two weeks off treatment. Patients achieving a complete response within the first two treatment cycles can receive up to three additional cycles of blinatumomab to a maximum of five cycles.

pERC made this recommendation because it considered there may be a net clinical benefit of blinatumomab based on demonstrated activity with the use of blinatumomab, the rates of complete remission and the rates of subsequent alloHSCT in a heavily pre-treated population and based on a substantial need for treatment options in this small population of pediatric patients who are in second or later relapse, who relapse after alloHSCT or who have refractory disease. However, pERC acknowledged there was considerable uncertainty in the magnitude of the clinical benefit due to limitations in the evidence

	from the available non-randomized clinical trial. In addition, pERC made this recommendation while acknowledging there was an absence of data on quality of life and that this treatment has considerable, but manageable, toxicities. pERC noted that the use of blinatumomab partially aligned with patient values as there is a substantial need for more effective treatment options for patients who have relapsed or refractory disease. However, pERC noted there are toxicities with blinatumomab, an intense administration schedule for patients and caregivers, and that the clinical benefit and impact of blinatumomab on patients' quality of life compared with other treatments is unknown. The Committee concluded that blinatumomab, at the submitted price and given the high level of uncertainty in the magnitude of long-term benefit, as well as the incomplete accounting for the complex resource intensity of administration, could not be considered cost-effective in pediatric patients with Ph− relapsed or refractory B precursor ALL.
POTENTIAL NEXT STEPS FOR STAKEHOLDERS	**Pricing Arrangements to Improve Cost-Effectiveness** Given pERC was satisfied that blinatumomab may have a net clinical benefit in pediatric patients with Ph− relapsed or refractory B precursor ALL who are in second or later relapse, who relapse after alloHSCT, or who have refractory disease, jurisdictions may want to consider pricing arrangements that would improve the cost-effectiveness of blinatumomab to an acceptable level. pERC noted the cost of blinatumomab was extremely high and that drug price was a key driver of the incremental cost-effectiveness estimates. Therefore, to offset the considerable uncertainty in the clinical effect estimates, pERC concluded that a substantial reduction in drug price would be required in order to improve cost-effectiveness. **Access to Expertise in Managing Side Effects** pERC noted that some of the potential neurological side effects of blinatumomab are severe, have life-threatening consequences, and require the expertise of hematologists experienced in dealing with these side effects. Therefore, pERC strongly supports restricting administration of blinatumomab to treatment centres that have the expertise to monitor and manage these potential side effects. **Resource Use and Adoption Feasibility** pERC noted that the preparation, administration, and management of blinatumomab is very resource-intensive. Therefore, pERC noted that jurisdictions will need to consider the incremental costs associated with, but not limited to, purchasing specialized infusion pumps, training pharmacy and nursing staff, coordinating outpatient and hospital resources, and monitoring and treating adverse events, all of which may require significant expenditures in human resources. **Wastage and Budget Impact Likely to Affect Adoption Feasibility** pERC expects that drug wastage will be a significant issue, given there is only one vial size for blinatumomab, and smaller doses are required for pediatric patients who weigh less than 45 kg. pERC also expects there will be considerable wastage with blinatumomab because of the challenges associated with implementing complex blinatumomab protocols (e.g. different infusion durations per preparation bag [between 24-96 hours], different pump infusion rates with different durations of infusion etc.). pERC agreed that jurisdictions will need to consider mechanisms to minimize wastage upon implementation of a reimbursement recommendation, including advocating for the availability of a smaller vial size, especially for the pediatric

population.

Collecting Evidence to Reduce Uncertainty in the Magnitude of Clinical Benefit and the Cost-Effectiveness of Blinatumomab
Given the considerable uncertainty in the magnitude of clinical benefit of blinatumomab in pediatric patients with Ph− relapsed or refractory B precursor ALL who are in second or later relapse, who relapse after alloHSCT, or who have refractory disease, pERC concluded that additional prospective evidence of long-term overall survival and alloHSCT eligibility should be collected to decrease the uncertainty in the incremental effect and cost-effectiveness of blinatumomab. pERC noted that, when such prospectively collected data become available, jurisdictions will need to review these new data.

Availability of Stabilizer
pERC noted that one vial of blinatumomab can be used to prepare more than one infusion bag, given the stability of the reconstituted vials and the prepared infusion bags. However, 5.5 mL of stabilizer is required to prepare each infusion bag and there are only 10 mL of stabilizer included with each package of blinatumomab. Thus, to prepare additional bags from one vial of drug, additional stabilizer is required from a different package. pERC agreed that stabilizer should be made available separately from the package of blinatumomab vial. Alternatively, a larger volume of stabilizer could be made available by the manufacturer to facilitate the preparation of more than one infusion bag per vial of drug.

SUMMARY OF pERC DELIBERATIONS

pERC's *Deliberative Framework* for drug reimbursement recommendations focuses on four main criteria:	
CLINICAL BENEFIT	PATIENT-BASED VALUES
ECONOMIC EVALUATION	ADOPTION FEASIBILITY

Acute lymphoblastic leukemia (ALL) is a highly aggressive hematological malignancy characterized by bone marrow infiltration and marrow failure. It is the most common pediatric malignancy, representing approximately 30% of all childhood cancers. There are approximately 600 cases of ALL in Canada per year, with the majority of cases occurring in young adults, adolescents, and children. Of those cases, approximately 70% are considered precursor B cell–derived. ALL is curable in up to 90% of pediatric cases with up-front treatment with sequential intensive multi-drug chemotherapy protocols. However, there is a small population of pediatric patients who experience induction failures: whose disease does not go into remission with conventional chemotherapy, or despite multiple lines of chemotherapy, or is considered refractory to chemotherapy, all of which have a very poor prognosis. Survival of this small population of relapsed/refractory patients are limited, and there is a significant unmet need for effective treatments for these patients. In contrast to up-front treatment with multi-drug chemotherapy protocols, pERC noted there is no consensus on the optimal standard treatment for pediatric patients with Philadelphia chromosome-negative (Ph−) relapsed or refractory B precursor ALL. Relapsed disease can be treated with three blocks of intense chemotherapy delivered in the in-patient setting. Patients can continue on multi-drug chemotherapy as a bridge to undergoing allogeneic hematopoietic stem cell transplant (alloHSCT), if a donor is available. Registered clinicians noted that available treatments after second or further subsequent relapse include off-study compassionate access to blinatumomab or experimental chimeric antigen receptor (CAR) T-cell therapy in a clinical trial setting. Input from registered clinicians noted there is no clear optimal therapy for patients with refractory disease and that these patients have very poor outcomes with traditional chemotherapy. Survival of this cohort of relapsed/refractory pediatric patients are limited. Therefore, pERC acknowledged there is a substantial need for treatment options to prolong survival in patients who are in second or later relapse, in patients who relapse after HSCT, and in patients who have refractory disease.

The Committee deliberated on the phase II results of one phase I/II non-randomized, non-comparative study (MT103-205) that evaluated the efficacy and safety of blinatumomab in pediatric patients with Ph− relapsed or refractory B precursor ALL. The Committee noted that only limited conclusions could be drawn from the MT103-205 trial because there was no direct randomized controlled trial (RCT) comparing blinatumomab with currently available treatment options. pERC considered the results of the MT103-205 trial, which showed encouraging complete remission rates and alloHSCT rates following treatment with blinatumomab in relapsed and refractory patients. However, pERC noted it was challenging to meaningfully interpret the overall survival benefit of blinatumomab because of the lack of comparative data in the available clinical trial. The Committee noted it was also challenging to determine how many patients were alive at the end of the trial and although there may have been a survival advantage to blinatumomab, pERC was uncertain if that advantage was attributable to treatment with blinatumomab or to some other factor. pERC noted that long-term survival in patients in this setting is uncommon, as the prognosis of these patients is poor following multiple relapses. Furthermore, pERC was unable to comment on the impact of blinatumomab on patients' quality of life because it was not measured in the MT103-205 trial. Therefore, while pERC agreed that there is demonstrated activity with blinatumomab, based on the rates of complete remission in the MT103-205 trial, there was considerable uncertainty in the magnitude of effect given the lack of comparative data, and the lack of long-term outcome data on outcomes important to patients, including transplant eligibility, quality of life, and overall survival. However, pERC acknowledged there is a significant unmet need for effective treatment options that prolong relapsed/refractory patients' survival; therefore, pERC agreed that there may be a net clinical benefit for this cohort of patients. The Committee also discussed that additional prospective evidence of long-term overall survival and alloHSCT eligibility should be collected to decrease the uncertainty about the magnitude of clinical benefit of blinatumomab compared with current treatment options. pERC noted that, when such prospectively collected data become available, jurisdictions will need to review these new data. The Committee further noted there are two ongoing clinical trials investigating blinatumomab compared to currently available treatment options in the first relapse setting. While pERC acknowledged that these trials do not include patients with multiple relapses or patients with refractory disease, pERC

expects these trials will provide clarity on the comparative effectiveness of blinatumomab compared chemotherapy in the relapsed setting.

pERC also considered the results of an unpublished historical cohort of pediatric patients provided by the submitter. pERC expressed several concerns with the comparability of the historical cohort to the MT103-205 study including, but not limited to, differences in important prognostic variables that were not adjusted for; small sample size with low power; missing data; and insufficient reporting of methodology. pERC discussed that, while the historical comparator provided by the submitter reported rates of complete remission similar to the MT103-205 trial, uncertainty remains due to the aforementioned limitations. Given the uncertainty in the presented data, pERC re-iterated its conclusion that the currently available data suggest there appears to be activity with blinatumomab; however, the magnitude of effect compared with available treatments is unknown.

pERC discussed the toxicity profile of blinatumomab and noted that severe cytokine-release syndrome and neurological toxicities are specific to treatment with blinatumomab. Given the absence of comparative data in the study, pERC considered the Clinical Guidance Panel's (CGP) clinical expertise and opinion regarding toxicities associated with blinatumomab. The CGP noted that cytokine-release syndrome and neurological toxicities are known to be associated with blinatumomab, but they are manageable and reversible. pERC also noted the CGP indicated that toxicities associated with blinatumomab are different than those associated with standard chemotherapy and, in particular, do not include the same incidence of infections. pERC also considered input from registered clinicians who noted that blinatumomab is associated with significantly fewer acute toxicities and fewer long-term side effects as well as fewer infection complications compared with current treatment options. Overall, pERC acknowledged that, while there are significant toxicities associated with blinatumomab, these toxicities can be managed by hematologists who have experience treating patients with blinatumomab.

pERC deliberated on the input from patient advocacy groups, which indicated that patients with ALL and their family members value disease control and the management of side effects related to current therapies and ALL. pERC discussed that patients also value more tolerable treatments that do not result in serious long-term effects or side effects that are difficult to manage. pERC expressed concerns about the adverse events that are specific to blinatumomab, including cytokine-release syndrome and neurological toxicities. However, the Committee acknowledged that these are known toxicities specific to blinatumomab that can be managed by experienced hematologists. pERC considered patient input that expressed that the severe side effects and toxicities that children experience also significantly impact the parents and siblings, who experience emotional pain when their child or sibling suffers. The Committee also acknowledged the significant emotional burden experienced by patients and their families when a child is treated for relapse. Furthermore, pERC acknowledged the significant financial burden caregivers face when they leave their jobs to care for their child. Therefore, pERC concluded that blinatumomab partially aligned with patient values because blinatumomab appears to have some activity, but the magnitude of the benefit is unknown, the treatment schedule is intense for patients and caregivers, and there are also considerable toxicities associated with blinatumomab, but these are tolerable and manageable.

pERC deliberated on the cost-effectiveness of blinatumomab and concluded that blinatumomab is not cost-effective when compared to standard of care salvage multi-drug chemotherapy. pERC noted that the pCODR Economic Guidance Panel's (EGP) best estimate of cost-effectiveness included a large range of incremental cost-effectiveness estimates (ICERs) that also included the submitter's best estimate. The Committee noted several limitations in the submitted analysis, particularly, the lack of comparative-effectiveness data and the resulting uncertainty in relative efficacy between blinatumomab and the multi-drug chemotherapy standard of care. pERC also considered that important clinical inputs that would potentially have an impact on the clinical effectiveness estimates could not be explored, including treatment duration with blinatumomab, the cost of treating adverse events, rates of HSCT (since patients receiving HSCT were not censored from the overall survival curve), and subsequent treatments. However, the Committee also noted that extending survival benefit beyond the trial period, assuming that patients with a complete remission past 60 months are cured and, therefore, will have the life expectancy of the general Canadian population, may have overestimated the long-term benefit anticipated with blinatumomab. Furthermore, pERC discussed that in the submitted model, it was assumed that most of the blinatumomab administration costs beyond the first cycle of treatment would be in an outpatient setting. Given that jurisdictions have limited experience with blinatumomab administration to date, many patients may have the majority of their blinatumomab treatment administered in hospital. pERC also agreed that the administration and health system costs were greatly underestimated, since only the nurse

visit to change patients' intravenous bags was incorporated in the model, which did not take into account the complex logistics of dose preparation and the time requirement involved with blinatumomab infusion for the health care system. The Committee also noted wastage was taken into account in the submitted model by assuming that only one pediatric patient is treated with blinatumomab at a given site at any time, thus vial sharing was not considered. However, it was noted by pERC that wastage is a significant concern as there is only one vial size of blinatumomab and dosages for pediatric patients will likely be smaller, especially for patients who weigh under 45 kg. pERC therefore agreed that the incremental cost of treatment with blinatumomab is likely substantially greater than incorporated in the economic model. pERC also noted that the submitted economic model has the potential for relatively large clinical effect gains, given that a pediatric patient can be cured and could continue to live more than 60 years beyond cure. Overall, pERC concluded that the incremental cost of blinatumomab is likely underestimated due to the substantial uncertainty in the comparative-effectiveness data; the assumption that blinatumomab, beyond the first cycle, would most often be administered in an outpatient setting; and that only the cost of a nurse to change the blinatumomab infusion bag was incorporated into the model for outpatient administration costs. pERC also agreed that blinatumomab has an extremely high cost and the submitted price would need a substantial price reduction for it to be considered cost-effective. The Committee agreed that the true ICER is likely substantially greater than the upper range of the EGP reanalysis estimate.

pERC considered the feasibility of implementing a reimbursement recommendation for blinatumomab. A number of implementation and feasibility challenges were discussed. Specifically, the requirement for considerable coordination of pharmacy and nursing staff training to prevent medication error for both in-patient and outpatient administration; the strict adherence to and intensive staff training for the complex preparation process that includes pre-coating infusion bags with the provided solution stabilizer; and the required monitoring and treatment of toxicities. pERC further emphasized that due to the complex preparation and administration protocol of blinatumomab, treatment will be limited to specialized tertiary centres with adequate resources available to prepare multiple bag changes (e.g., specialized programmable and lockable infusion pumps, adequate staffing). In addition, pERC noted that although blinatumomab can be administered on an out-patient basis, many pediatric patients may be treated in-hospital beyond the initial cycles of therapy, due to logistical and local resource reasons. Any outpatient treatment will require extensive coordination amongst inpatient and outpatient facilities and the availability of on-call support. The complex administration process of blinatumomab was further discussed by pERC, since several variations of concentrations and durations of stability are possible when preparing blinatumomab. It was noted that different jurisdictions may adopt different administration and preparation protocols for blinatumomab in order to accommodate local resources. pERC further emphasized that due to the complex preparation and administration protocol for blinatumomab, treatment should be limited to specialized tertiary centres with adequate resources available. Furthermore, pERC agreed with the Provincial Advisory Group (PAG) that there is the potential for wastage, as there is only one vial size of blinatumomab available, and that pediatric patients under 45 kg will require a smaller dose. In addition, the PAG noted that, while it is possible that one vial could be used to prepare more than one infusion bag, 5.5 mL of stabilizer is required to prepare each infusion bag. As only 10 mL are included with each package of blinatumomab, additional stabilizer is required from a different package in order to prepare additional bags from one vial of drug. pERC discussed that additional stabilizer should be made available separately from the package of the blinatumomab vial in order to minimize wastage. Alternatively, a larger volume of stabilizer could be made available by the manufacturer to facilitate more than one infusion bag preparation per vial of drug. Considering the number of implementation challenges, pERC agreed that implementing a reimbursement recommendation for blinatumomab will require considerable expenditures and additional human resources that are not accounted for in the cost-effectiveness model provided by the submitter. Due to these additional costs, pERC agreed that the budget impact of blinatumomab will be substantially greater than what was estimated in the submitted budget impact analysis.

EVIDENCE IN BRIEF

The CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) deliberated on the following:

- a pCODR systematic review
- an evaluation of the manufacturer's economic model and budget impact analysis
- the guidance from the pCODR clinical and economic guidance panels
- a joint submission from a patient advocacy group (Advocacy for Canadian Childhood Oncology Research Network (Ac2orn), the Leukemia & Lymphoma Society of Canada, and Ontario Parents Advocating for Children with Cancer
- input from registered clinicians
- input from pCODR's Provincial Advisory Group (PAG).

OVERALL CLINICAL BENEFIT

pCODR review scope

The purpose of the review is to evaluate the efficacy and safety of blinatumomab as a monotherapy, compared with an appropriate comparator, on patient outcomes in the treatment of pediatric patients with Philadelphia chromosome–negative (Ph–) relapsed or refractory B precursor acute lymphoblastic leukemia (ALL).

Studies included one non-randomized, non-comparative trial

The pCODR systematic review included one phase I / II non-randomized trial, MT103-205, which was a dose-finding and efficacy trial that evaluated the efficacy and safety of blinatumomab in pediatric patients with Ph– relapsed or refractory B precursor ALL.

The phase I portion of the trial established a stepwise dosage of 5μg/m^2 per day for one week, followed by escalation to 15 μg/m^2 per day for the remaining infusion days, which was the recommended dosage of blinatumomab in children with relapsed and refractory ALL for the phase II portion of the trial. Treatment with blinatumomab was administered as a four-week continuous infusion, followed by two weeks off treatment, and involved stepwise 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) for the remaining three weeks of cycle 1 and subsequent cycles. Patients achieving a complete remission within the first two treatment cycles could receive up to three additional cycles of blinatumomab (five-cycle maximum). 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 the remaining cycles.

Key inclusion criteria required that patients have refractory or relapsed ALL. Refractory was defined as patients who have not achieved a first remission and have failed a full standard induction regimen (i.e., primary refractory), 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. Relapse was defined as any marrow relapse after allogeneic hematopoietic stem cell transplantation (alloHSCT) or second or later bone marrow relapse. Pediatric patients were required to be less than 18 years of age with precursor B-cell ALL with greater than 25% bone marrow blasts, Ph– or positive, and a Karnofsky or Lansky (age less than 16 years) performance status of greater than 50%. Key exclusion criteria included active acute or extensive chronic graft-versus-host disease after HSCT, active or extensive central nervous system or testicular involvement, previous treatment with blinatumomab, and any HSCT within three months prior to receiving blinatumomab treatment.

The criteria of the pCODR systematic review required mixed-design clinical trials to report efficacy results separately, by phase. Thus, data requests were made to the submitter for the key secondary outcomes that were not reported separately. However, considering the small sample size of the phase II portion (n = 44), the identical blinatumomab dosing design and inclusion criteria, and the fact that pooled analyses were pre-planned (although considered exploratory and used for Health Canada regulatory submissions), the pooled data were included in the Clinical Guidance Report for reference, but the primary focus of the efficacy results is based on the phase II portion of the trial.

Patient populations: Majority of patients with at least two relapses and refractory to prior treatment

Study MT103-205 enrolled 70 patients with relapsed and refractory Ph– B-cell ALL. Forty-four patients were enrolled in the phase II portion of the trial. The median age of patients was 10.5 years and the majority of patients were treated in European centres (71%), were male (73%), were white (75%), had at least two relapses (50%), had previous alloHSCT (57%), and were primary refractory (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.

Key efficacy results

The key efficacy outcome deliberated on by pERC included complete remission (CR) within the first two cycles of treatment, overall survival (OS), and the percentage of patients who received an alloHSCT after treatment with blinatumomab.

The CR rate within the first two cycles of treatment with blinatumomab in the phase 2 portion of the MT103-205 trial was 32% (95% confidence interval [CI], 19 to 48). pERC agreed with the Clinical Guidance Panel's (CGP) opinion that the rates of complete remission observed in the trial were similar to response rates observed with current treatment options. Among the patients achieving CR after treatment with blinatumomab, 30% of patients (n = 13 out of 44) went on to receive alloHSCT. Of these patients, five (11%) were in a blinatumomab-induced CR (patients received blinatumomab and may have received other treatment, including HSCT), and two (5%) were in a CR after receiving only blinatumomab.

For patients in the phase II portion of the trial, the median follow-up time was 11.6 months, with a median OS of 8.2 months (95% CI, 4.0 to 14.6). pERC noted that it was challenging to meaningfully interpret the OS benefit of blinatumomab because of the lack of comparative data in the available clinical trial. The Committee noted that it was challenging to determine how many patients were alive at the end of the trial and whether the long-term survival advantage could be attributed to treatment with blinatumomab due to the non-randomized, non-comparative study design.

In the absence of comparative efficacy data, pERC considered results from an historical comparator and the clinical opinion of the CGP. pERC noted that the currently available data suggest there appears to be activity with blinatumomab; however, the magnitude of effect compared with available treatments is unknown.

Patient-reported outcomes not measured

Quality of life was not measured in the MT103-205 trial; as such, pERC was unable to comment on the impact of blinatumomab on quality of life.

Safety: Significant toxicities requiring intensive specialized management

Assessment of adverse events (AEs) was carried out on all patients from phase I and II (n = 70) who received any infusion of blinatumomab at the recommended dose of 5/15 $\mu g/m^2$ per 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 frequent grade ≥ 3 AEs were primarily cytopenias, including anemia (36%), thrombocytopenia (21%), neutropenia (17%), and febrile neutropenia (17%). Liver function parameters, including alanine aminotransferase (ALT) (n = 13), aspartate aminotransferase (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-alloHSCT after blinatumomab-induced remission. These deaths were preceded by multi-organ failure, sepsis, and respiratory failure.

Treatment-emergent AEs (TEAEs) occurred in all patients (all grades = 100%; grade ≥ 3 = 87%) and serious TEAEs occurred in 56% of patients (grade ≥ 3 = 28%). The most frequent TEAEs were 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 multi-organ failure, sepsis, fungal infection, recurrent leukemia, disease progression, respiratory failure, and thrombocytopenia. TEAEs led 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. In 84% of patients, TEAEs were judged related to treatment with blinatumomab (54% were grade ≥ 3).

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 to 16.0). Treatment of these patients was either interrupted (n = 2) or permanently discontinued (n = 2); however, all four achieved a CR at the 12-week response assessment. pERC noted that the CGP indicated that cytokine-release syndrome and neurological events are specific to blinatumomab, and that these AEs are manageable by experienced hematologists and reversible by prophylactic use of dexamethasone, or by stopping blinatumomab.

Limitations: No direct comparative data with currently available therapies

pERC discussed several limitations in the MT103-205 trial in using blinatumomab in pediatric patients with Ph− relapsed or refractory B precursor ALL. This study was non-comparative; thus, there is substantial uncertainty regarding the magnitude of benefit with blinatumomab compared with other current therapies. pERC further discussed the limitations of non-randomized, non-comparative studies and considered that the conclusions that can be drawn from non-randomized, non-comparative data are not as robust as those that can be drawn from randomized controlled trials. pERC considered that there are currently no randomized controlled trials underway in a heavily pre-treated multiple relapse/refractory population. However, pERC noted two current ongoing phase III randomized controlled studies investigating blinatumomab compared with chemotherapy in the first relapse setting, which should confirm the role of blinatumomab in the relapse setting.

pERC also discussed the contextual information on the results from Study 20140228, which provided historical efficacy data on treatments used for pediatric patients with Ph− relapsed or refractory B precursor ALL. pERC considered the results of this analysis and noted several limitations. While statistical methods were used to adjust for differences in prognostic variables between Study 20140228 and MT103-205, pERC agreed that not all important prognostic variables that may have an impact on the estimates of efficacy between the two cohorts were adjusted for. Additionally, pERC noted the small sample size, missing data, and the insufficient reporting of methodology. Overall, pERC agreed with the Methods team and the CGP that the historical data must be interpreted with caution.

Need and burden of illness: More effective treatment options for pediatric Ph− relapsed or refractory B precursor acute lymphoblastic leukemia

ALL is a highly aggressive hematological malignancy characterized by bone marrow infiltration and marrow failure. It is the most common pediatric malignancy, representing approximately 30% of all childhood cancers. There are approximately 600 cases of ALL in Canada per year, with the majority of cases occurring in young adults, adolescents, and children. Of these cases, approximately 70% are considered precursor B cell–derived. ALL is curable in up to 90% of pediatric cases with up-front treatment with sequential intensive multi-drug chemotherapy protocols. However, there is a small population of pediatric patients who experience induction failures whose disease does not enter remission with conventional chemotherapy, whose disease is considered refractory to chemotherapy, or who experience multiple disease relapses all of which are associated with very poor prognosis. Survival of this small population of relapsed/refractory patients are limited, and there is a significant need for effective treatments for these patients. In contrast to up-front treatment with multi-drug chemotherapy, pERC noted there is no consensus on the optimal standard treatment for pediatric patients with Ph− relapsed or refractory B precursor ALL. Relapsed disease can be treated with three blocks of intense chemotherapy delivered in the in-patient setting. Patients can continue on multi-drug chemotherapy or proceed to alloHSCT if a donor is available. Other available treatments after second or further relapse include off-study compassionate access to blinatumomab, or experimental chimeric antigen receptor (CAR) T-cell therapy in a clinical trial setting. Therefore, there is a significant need for effective treatment options that prolong patients' survival.

Registered clinician input: Need for effective treatments with fewer side effects

The Committee deliberated on input from two clinicians. According to this input, clinicians noted that the occurrence of ALL is the most common pediatric malignancy, and blinatumomab would allow patients to receive therapy at relapse with significantly less acute and fewer long-term side effects compared with current treatment options. Clinicians noted that blinatumomab can replace conventional therapy in the relapsed and refractory setting. There are no defined current standard treatment in the Canadian setting for relapsed or refractory ALL. Current options in the Canadian setting were identified to be three blocks of intense in-patient chemotherapy, followed by HSCT. Registered clinicians indicated that the current treatment for disease with multiple relapses is mainly obtained through clinical trials or compassionate

access. Furthermore, registered clinicians note there is no clear optimal therapy for patients with refractory disease, and that these patients have very poor outcomes with traditional chemotherapy. Therefore, survival of this cohort of relapsed/refractory pediatric patients is limited. With regard to the benefits of blinatumomab, registered clinicians indicated that it is better tolerated and associated with long-term toxicities compared with chemotherapy, by patients with most types of comorbidities or active infections. pERC noted that jurisdictions will need to manage the training of staff on the management of toxicities during implementation of blinatumomab. Registered clinicians also indicated that blinatumomab offers the potential option of having most of the treatment delivered on an outpatient basis. Given the considerable challenges to implementing outpatient treatment, as outlined by the Provincial Advisory Group, pERC agreed that most patients will likely be treated with blinatumomab as in-patients. The clinicians providing input also 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 fewer toxicities and has far fewer infectious complications and end-organ damage. In addition, blinatumomab reduces the need for hospitalizations and transfusions and can be a bridge to alloHSCT. The clinicians providing input noted that blinatumomab has a distinct mechanism of action for patients with refractory disease that has failed to respond to conventional chemotherapy.

PATIENT-BASED VALUES

Values of patients with acute lymphoblastic leukemia: Quality of life, symptom and disease control, disease remission, fewer side effects

pERC deliberated on patient advocacy group input. Twelve caregivers, one of whom had direct experience with blinatumomab, responded to the surveys and interviews. The Committee noted that patients experience various disease-related symptoms that have a large impact on their daily lives. Caregivers reported that relapsed and refractory disease presents with pain and fatigue and that the most challenging limitations of treatment is immunosuppression. Being more susceptible to illness limits interactions with others and limits a child's 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, attend school, visit family, and take part in many other activities during the first three phases of treatment. Additionally, mood changes, neuropathy, enlarged lymph nodes, weakness, bruising, pain, nausea, vomiting, and fatigue were identified as symptoms that pediatric patients commonly experience. Patient advocacy group input further indicated that ALL is fatal if left untreated and there are limited treatment options currently available for pediatric patients. Overall, disease-related symptoms were reported to have a significant impact on patients' and families' daily lives.

Patient input expressed that severe side effects and toxicities must be managed by parents, who experience emotional pain when their child suffers. pERC acknowledged the significant emotional burden for both patients and families who experience emotional pain when their child suffers because of the disease. Input from caregivers also noted that parents have to leave their jobs to care for their child, which may lead to financial issues caused by a combination of loss of income and the cost of paying for medication, travel, and care for other siblings. pERC noted the significant financial burden that is associated with caring for a child with ALL. Caregivers also indicated they do not have time to care for themselves, and often their mental health is impacted by stress, fear, worry, depression, anxiety, and uncertainty.

Patient values on treatment: More treatment options, manageable and tolerable treatment-related side effects

Input from patients' caregivers indicated that the main treatments used to treat relapsed/refractory ALL are drug therapies and radiation. Caregivers reported their children having some variation of side effects associated with their treatments. Common side effects of the current treatments include immunosuppression, severe neuropathic pain, severe insomnia, lumbar punctures, mood changes, neuropathy, nausea and vomiting, hyperactive or hypoactive behaviour, loss of appetite or overeating, depression/sadness, gastrointestinal tract damage/mucositis, diarrhea, headache, weight loss or gain, fever, hair loss, infections, steroid-induced diabetes, and psychosis.

pERC noted that patients and their families value treatments that will provide disease and symptom control. Caregivers expect that blinatumomab may provide an opportunity for a patient to achieve disease remission, stop disease progression, manage disease-related symptoms, and improve quality of

life. Caregivers value treatment that will achieve remission or stop progression more effectively to achieve a more tolerable quality of life for both the child and their family members. Caregivers expressed the desire that treatment have short-term, manageable side effects. Additionally, caregivers expressed that patients would be willing to tolerate a number of side effects with blinatumomab; however, they expressed that treatment should not result in serious long-term toxicities and illnesses, or result in side effects that are difficult to manage, such as extreme pain.

Overall, pERC noted that management of side effects related to current therapies and the improvement of quality of life is important to patients and their families. While significant toxicities associated with blinatumomab, such as cytokine-release syndrome and neurological complications, do not align with patient values, pERC agreed that achieving remission and having a treatment option with more tolerable and manageable side effects that may improve quality of life are important to patients and their families.

ECONOMIC EVALUATION

Economic model submitted: Cost-utility analysis

The cost-effectiveness analysis and cost-utility analysis submitted to pCODR by the manufacturer compared blinatumomab with currently available treatments for pediatric patients with Ph– relapsed or refractory B precursor ALL. The comparator comprised the standard of care, which consists of salvage multi-drug chemotherapy. The economic evaluation was based on non-comparative data with statistical adjustments to make the baseline patient characteristics similar between MT103-205 and a historical cohort study (study 20140228).

Basis of the economic model: Historical control used as a comparator in cost-utility analyses

The submitted model was a partitioned-survival model comprised of three distinct health states, including remission (complete remission), progressive disease (includes progressive disease, aplastic bone marrow, and partial remission), and death. Patients who survived for 60 months in the treatment phase were assumed to be cured.

Given the lack of long-term, direct comparative data, there was considerable uncertainty in the clinical inputs for the economic evaluation. A historical cohort study was provided and statistical adjustments were used to derive indirect comparative efficacy data for all of the efficacy inputs used in the economic model. Key costs considered in the analysis provided by the submitter included cost due to drug acquisition, in-patient administration of treatment, nurse visits for intravenous-bag change, stem cell transplantation, palliative care, and wastage. The key clinical outcome was overall survival (based on study MT103-205 and a historical cohort) and utility values were derived from a preference elicitation study in the UK, using time trade-off.

The Committee discussed the various implementation challenges in administering blinatumomab in the outpatient setting, and agreed that many patients are likely to be treated as in-patients until jurisdictions develop greater experience with blinatumomab treatment. Based on the submitted model, patients are in hospital only for the first 28 days of the first cycle and the first two days of the second cycle. The Committee also noted wastage was taken into account in the submitted model by assuming that only one pediatric patient is treated with blinatumomab at a given site at any time, as vial sharing was not considered. pERC therefore agreed that the incremental cost of drug administration is substantially underestimated. pERC also agreed that the administration and health system costs were underestimated, since only the nurse visit to change patients' intravenous bags was incorporated into the model, and thus did not take into account the complex logistics of dose preparation and time requirement involved with blinatumomab infusions. However, the cost of the programmable, lockable infusion pump was incorporated into the model.

Drug costs: Very high drug costs, especially compared with salvage therapy

The unit cost of blinatumomab is $2,978.26 per 38.5 μg of lyophilized powder in a single-use vial for reconstitution. In the MT103-205 trial, on average, subjects initiated two cycles of blinatumomab and consumed 1.4 cycles, which corresponds to 39 vials (assuming one vial per day on blinatumomab treatment). The cost of 39 vials is $116,152.

There is no established standard of care for pediatric patients with relapsed or refractory Ph– ALL. The most frequently used therapy consists of salvage multi-drug chemotherapy. Based on cost data from QuintilesIMS DeltaPA, the cost for initial induction and two consolidation blocks is as follows:

- UK R3 ALL: $6,469.81
- COG-AALL 1331: $15,605.91
- COG-AALL 0031: $11,004.95.

Based on cost data from QuintilesIMS DeltaPA, the cost of clofarabine is $128.96 per mg or $31,852.01 per phase.

In the submitted model, the unit costs of each component of the chemotherapy regimens were based on cost data from McKesson Canada and the Ontario Drug Benefit Formulary, as well as from Canadian distributors and manufacturers. The average cost for the combined therapies was $11,246.

In that model, the cost for initial induction and two consolidation blocks is as follows:

- UK R3 ALL: $13,678.73
- COG-AALL 1331: $16,371.77
- COG-AALL 0031: $3,686.60.

The cost of clofarabine was not included in the submitted base case. Based on information from the manufacturer of clofarabine, the total cost of clofarabine is $128.96 per mg or $31,885.54 per phase.

Cost-effectiveness estimates: Substantial uncertainty due to no direct comparative data, extrapolation of overall survival benefit

pERC deliberated on the economic analysis submitted, which provided estimates on the cost-effectiveness of blinatumomab compared with multi-drug chemotherapy. pERC noted that the submitter derived the comparative efficacy data using the MT103-205 study and a historical cohort study. The submitter's best estimate of the incremental cost-effectiveness ratio (ICER) is $15,940 per quality-adjusted life-year (QALY).

pERC noted there was substantial uncertainty in the magnitude of the clinical benefit associated with blinatumomab compared with the historical data. This made it challenging to estimate the incremental effect of treatment with blinatumomab and, therefore, the resulting incremental cost-effectiveness of blinatumomab. The Committee also noted that a number of clinical assumptions in the submitted model may overestimate the long-term benefit anticipated with treatment with blinatumomab. Specifically, pERC noted that the extrapolation of the survival benefit beyond the trial period and the utility for long-term survival had a substantial impact on the ICER. pERC noted that the submitter included overall survival data for blinatumomab based on 20 months of follow-up, and not the final analysis, using 24 months of follow-up. The submitter noted that the median overall survival was the same from both the primary and final analyses and the submitter claimed that modelling based on 24 months of follow-up would not differ materially. Since survival was captured only to month 20 in the primary analysis of the MT103-205 trial, the survival curve of blinatumomab was extrapolated from 20 to 60 months. Patients alive at 60 months were considered to be cured of the disease and to have the life expectancy of the general Canadian population from that time forward. pERC noted that the main factors that influence the incremental costs include hospital length of stay for blinatumomab or standard of care, the cost per day for an in-patient stay, and the number of vials of blinatumomab consumed. The Committee noted there is uncertainty on how long pediatric patients would remain on treatment with blinatumomab. Given that treatment duration was not modifiable in the submitted model, the impact on increasing or decreasing the treatment duration is unknown. The main factors that influence the incremental effectiveness of blinatumomab are the hazard ratios for overall survival and the utility for long-term survival. Expert opinion was used for several inputs used in the economic model, including drug administration as an in-patient. The use of expert opinion is open to several limitations. Furthermore, AEs were not considered in the model and any disutility associated with an AE was not captured. Subsequent treatments were also not considered in the model. Although a number of patients may go on to receive HSCT after treatment with blinatumomab, not all patients would, and many subsequent treatments would be considered experimental and would vary. Despite these limitations, the pCODR Economic Guidance Panel (EGP) elected to continue with reanalysis estimates, as there are currently no comparative-effectiveness data, which would address many of the above limitations in the model.

pERC considered the EGP's reanalyses of the submitted model and noted that the EGP made the following changes to the model: The time horizon was reduced from 95 years to 70 years from cure; changes were made to the comparator to include clofarabine as a possible comparator; the COG-ALL 0031 regimen was excluded (the CGP noted this regimen is not commonly used in the relapse/refractory setting); the lower and upper bound of the overall survival hazard ratios were used to explore uncertainty of the anticipated overall survival; and hospital length of stay during treatment with blinatumomab was increased to 60 days, since treatment as an outpatient may not be feasible for some centres due to limited resources, and those patients would require hospitalization beyond the first cycle of treatment. These changes resulted in an ICER ranging from $6,577 per QALY to $100,948 per QALY. pERC noted that the ICER of blinatumomab is likely underestimated due to the substantial uncertainty in the comparative-effectiveness data, the assumption that most treatments will be given in an outpatient setting, and the fact that only the cost of a nurse changing the blinatumomab infusion bag was incorporated in the model for administration costs. pERC also noted that the considerable uncertainty in the comparative effectiveness cannot be captured in the EGP reanalysis and therefore is not fully captured in the EGP's range of ICER estimates. For example, it was noted that if there were no survival benefit with blinatumomab compared with multi-drug chemotherapy, the ICER would approach $9 million per QALY, which is substantially higher than the EGP's upper ICER estimate. pERC also agreed that the economic model has the potential for relatively large magnitude of clinical effect gains, since a patient could be cured and continue to live for more than 60 years. Overall, pERC agreed that blinatumomab cannot be considered cost-effective and will require a substantial price reduction to manage the cost-effectiveness and uncertainty related to clinical effect estimates.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: Small patient population, high drug cost, significant wastage; resource-intensive implementation

The Committee discussed factors affecting the feasibility of implementing a reimbursement recommendation for blinatumomab. Input from the PAG highlighted various challenges to implementing blinatumomab. These included the requirement for considerable training and coordination of pharmacy and nursing staff to prevent medication error, strict adherence to and intensive staff training for the complex preparation process that includes pre-coating infusion bags with the provided solution stabilizer and various protocols and rates of infusion depending upon the frequency that infusion bags will be changed, and monitoring and treating of toxicities. These concerns are supported by input from registered clinicians, who indicated that the toxicities observed with blinatumomab are different from chemotherapy. Therefore, strict adherence to the toxicity-management protocols will be important to manage treatment-related toxicities.

Various implementation and feasibility challenges were discussed, including, but not limited to, the requirement for considerable coordination of pharmacy and nursing staff training to prevent medication error for both in-patient and outpatient administration; the strict adherence and intensive staff training for the very complex preparation process that includes pre-coating infusion bags with the provided solution stabilizer; and the required monitoring and treatment of toxicities. pERC further noted that the complex preparation and administration of blinatumomab, may be limited to treatment centres that have adequate resources (e.g., appropriate supply of ambulatory infusion pumps, adequate staffing). In addition, pERC noted that many patients may have to be treated as in-patients beyond the initial cycles of treatment due to limited resources. However, any outpatient administration of blinatumomab will require coordination with in-patient and outpatient facilities, and ensuring the availability of on-call support for patients should issues arise with the infusion pumps. It will also require frequent patient visits to treatment centres to coordinate the changing of blinatumomab infusion bags or the proper programming of electronic infusion pumps. The complexity of blinatumomab treatment was further discussed by pERC since blinatumomab preparations may vary in concentrations and durations of stability, and it was noted that different jurisdictions may adopt different administration and preparation protocols in order to accommodate local resources. For instance, some jurisdictions may choose to supply blinatumomab every 96 hours, while others may adopt different infusion durations (e.g., every 48 hours or every 72 hours), all of which require different infusion rates, depending on the concentration of blinatumomab in the prepared product. Furthermore, pERC noted there is potential for wastage, as there is only one vial size of blinatumomab available, and pediatric patients will require a smaller dosage if they weigh less than 45 kg. pERC noted that a smaller vial size should be made available to minimize wastage for the smaller dosages used in pediatric patients. The Committee also noted that one vial of

blinatumomab can be used to prepare more than one infusion bag, given the stability of the reconstituted vials and the prepared infusion bags. However, 5.5 mL of stabilizer is required to prepare each infusion bag and there are only 10 mL of stabilizer included with each package of blinatumomab. Thus, to prepare additional bags from one vial of drug, additional stabilizer is required from a different package. pERC agreed that stabilizer should be made available separately from blinatumomab, or alternatively, a larger volume of stabilizer should be made available by the manufacturer to facilitate the preparation of more than one infusion bag per vial of drug. Based on these various challenges, pERC agreed that the implementation of blinatumomab will require considerably higher expenditures and more human resources than were accounted for in the economic model provided by the submitter. pERC further agreed that the budget impact of blinatumomab will increase due to these various additional costs.

DRUG AND CONDITION INFORMATION

Drug Information	• First-in-class bispecific T-cell engaging (BiTE) antibody construct
	• 38.5 μg per vial
	• Dosages for patients weighing less than 45 kg (body surface area-based dose), Cycle 1 is as follows:
	  • Days 1-7: 5 μg/m^2/day (not exceed 9 μg/day)
	  • Days 8-28: 15 μg/m^2/day (not to exceed 28 μg/day)
	  • Days 29-42: No treatment
	Subsequent cycles are as follows:
	  • Days 1-28: 15 μg/m^2/day (not to exceed 28 μg/day) throughout the entire 4-week treatment period.
	  • Days 29-42: No treatment
	For patients weighing greater than or equal to 45 kg (fixed dose), Cycle 1 is as follows:
	  • Days 1-7: 9 μg/day
	  • Days 8-28: 28 μg/day
	  • Days 29-42: No treatment
	Subsequent cycles are as follows:
	  • Days 1-28: 28 μg/day
	  • Days 29-42: No treatment

Cancer Treated	• Philadelphia chromosome-negative relapsed/refractory B precursor acute lymphoblastic leukemia (ALL)
Burden of Illness	• 10% to 20% of pediatric cases of Ph- B-ALL are relapsed or refractory • Significant symptom burden on patients and quality-of-life impact • Prognosis of patients is poor and prolonged survival is rare
Current Standard Treatment	• Salvage multi-drug chemotherapy followed by alloHSCT, where possible
Limitations of Current Therapy	• Limited impact on long-term prognosis as most patients eventually succumb to their disease.

ABOUT THIS RECOMMENDATION

The pCODR Expert Review Committee

Recommendations are made by the CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) following the pERC *Deliberative Framework*. pERC members and their roles are as follows:

Dr. Maureen Trudeau, Oncologist (Chair)
Dr. Paul Hoskins, Oncologist (Vice-Chair)
Dr. Scott Berry, Oncologist
Dr. Kelvin Chan, Oncologist
Dr. Matthew Cheung, Oncologist
Dr. Craig Earle, Oncologist
Dr. Allan Grill, Family Physician
Don Husereau, Health Economist
Dr. Anil Abraham Joy, Oncologist
Karen MacCurdy Thompson, Pharmacist
Valerie McDonald, Patient Member Alternate
Carole McMahon, Patient Member
Dr. Catherine Moltzan, Oncologist
Jo Nanson, Patient Member
Dr. Marianne Taylor, Oncologist
Danica Wasney, Pharmacist

All members participated in deliberations and voting on the Initial Recommendation, except:

- Valerie McDonald, who did not vote due to her role as a patient member alternate.
- Don Husereau, Dr. Scott Berry, and Dr. Allan Grill, who were not present for the meeting.

Avoidance of conflicts of interest

All members of the pCODR Expert Review Committee must comply with the *pCODR Conflict of Interest Guidelines*; individual conflict-of-interest statements for each member are posted on the pCODR website, and pERC members have an obligation to disclose conflicts on an ongoing basis. For the review of blinatumomab (Blincyto) for pediatric acute lymphoblastic leukemia (ALL), through their declarations, one member had a real, potential, or perceived conflict and, based on application of the *pCODR Conflict of Interest Guidelines*, one member was excluded from voting.

Information sources used

pERC is provided with a pCODR Clinical Guidance Report and a pCODR Economic Guidance Report, which include a summary of patient advocacy group and Provincial Advisory Group input, as well as original patient advocacy group input submissions, to inform its deliberations. pCODR guidance reports are developed following the pCODR review process and are posted on the pCODR website. Please refer to the pCODR guidance reports for more detail on their content.

Consulting publicly disclosed information

pCODR considers it essential that pERC base its recommendations on information that may be publicly disclosed. All information provided to the pCODR Expert Review Committee for its deliberations was handled in accordance with the *pCODR Disclosure of Information Guidelines*. There was no non-disclosable information in this Recommendation document.

Use of this recommendation

This Recommendation from pERC is not intended as a substitute for professional advice, but rather to help Canadian health systems leaders and policy-makers make well-informed decisions and improve the quality of health care services. While patients and others may use this Recommendation, it is for informational and educational purposes only, and should not be used as a substitute for the application of clinical judgment respecting the care of a particular patient, for professional judgment in any decision-making process, or for professional medical advice.

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