

7.02 BLINATUMOMAB,

Powder for I.V. infusion 38.5 micrograms,

Blincyto[®], Amgen.

1 Purpose of Application

- 1.1 The resubmission requested Section 100 Authority Required (Efficient Funding of Chemotherapy) listing for blinatumomab for the treatment of patients with B-cell precursor acute lymphoblastic leukaemia (B-ALL) in haematological complete remission with minimal residual disease (MRD) following induction chemotherapy. The PBAC previously considered blinatumomab at the July 2018 meeting for this listing.
- 1.2 Listing was requested on a cost-effectiveness basis compared to consolidation chemotherapy.

Table 1: Key components of the clinical issue addressed by the submission

Component	Description
Population	Patients with B-ALL in haematological complete remission with minimal residual disease after receiving induction chemotherapy
Intervention	Blinatumomab continuous intravenous infusion 28 micrograms daily for 28 days delivered at a constant flow rate, followed by 14 days treatment free (one treatment cycle).
Comparator	Standard of care consolidation chemotherapy – post-induction
Outcomes	Relapse-free survival, overall survival and safety
Clinical claim	Superior effectiveness (statistically significant improvement in relapse free survival and numerical improvement in overall survival) and non-inferior safety for patients treated with blinatumomab compared to patients treated with standard of care chemotherapy - post induction

Source: Table 10, p.29 of the resubmission.

Abbreviations: B-ALL, B-cell precursor acute lymphoblastic leukaemia.

2 Requested listing

- 2.1 Blinatumomab was recommended for listing for relapsed/refractory Philadelphia chromosome negative (Ph-) B-ALL in July 2016 and November 2016 and was listed on the PBS in May 2017.
- 2.2 Blinatumomab was rejected for listing at the July 2018 meeting for patients with B-ALL in haematological complete remission with MRD following induction chemotherapy, on the basis of the patient population in the Australian setting not being well defined, the difficulty in estimating the incremental benefit and comparative safety versus standard of care chemotherapy and a high and uncertain incremental cost-effectiveness ratio (Blinatumomab Public Summary Document (PSD) July 2018, para 7.1).
- 2.3 An abridged version of the requested restriction is outlined below. Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough

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Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for	Proprietary Name and Manufacturer
BLINATUMOMAB 38.5 µg, injection, 1 vial	784 µg	31	\$81,417.39 (public)	Blincyto® Amgen Pty Ltd Australia
BLINATUMOMAB 38.5 µg, injection, 1 vial	784 µg	31	\$82,594.79 (private)	Blincyto® Amgen Pty Ltd Australia

Category / Program	Section 100 – Efficient funding of Chemotherapy (S100 EFC Public) Section 100 – Efficient funding of Chemotherapy (S100 EFC Private)
Prescriber type:	<input checked="" type="checkbox"/> Medical Practitioners
Condition:	Acute lymphoblastic leukaemia (ALL)
PBS Indication:	Minimal residual disease (MRD) positive B-cell precursor acute lymphoblastic leukaemia (B-ALL) in patients with complete haematological remission
Treatment phase:	Initial <i>treatment</i>
Restriction Level / Method:	<input checked="" type="checkbox"/> Authority Required - In Writing
Treatment criteria:	Must be treated by a physician experienced in the treatment of haematological malignancies.
Clinical criteria:	The treatment must be the sole PBS-subsidised therapy for this condition, AND The condition must be B-cell precursor acute lymphoblastic leukaemia with an Eastern Cooperative Oncology Group (ECOG) performance status of less than 2 AND The condition must not be present in the central nervous system or testis AND Patient must have received intensive combination chemotherapy for initial treatment of ALL or for subsequent salvage therapy AND The condition must have less than 5% blasts in bone marrow <i>Patient must have achieved a complete remission</i> AND Patient must have minimal residual disease defined as at least 10 ⁻⁴ (0.01%) blasts based on measurement in bone marrow, documented after an interval of at least 2 weeks from last systemic chemotherapy AND <i>Minimal residual disease must be measured using polymerase chain reaction or flow cytometry,</i> AND The treatment must not be more than two treatment cycles under this restriction in a lifetime
Caution	Careful monitoring of patients is required due to risk of developing life-threatening Cytokine Release Syndrome, neurological toxicities and reactivation of John Cunningham virus (JC) viral infection.

Treatment phase:	Continuing treatment
Restriction:	<input checked="" type="checkbox"/> Authority Required - Telephone
Treatment criteria:	Must be treated by a physician experienced in the treatment of haematological malignancies.
Clinical criteria:	Patient must have previously received PBS-subsidised initial treatment with this drug for this condition, AND <i>Patient must have achieved a complete remission,</i>

	<p>AND Patient must be MRD negative defined as either undetectable using the same assay as used to determine original eligibility or less than 10^{-4} (0.01%) blasts based on measurement in bone marrow, AND Patient must not develop disease progression while receiving PBS-subsidised treatment with this drug for this condition, AND The treatment must not be more than two treatment cycles under this restriction in a lifetime.</p>
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- 2.4 The resubmission proposed the same special pricing arrangement as in the previous submission, consisting of a [REDACTED] % rebate on the published AEMP per vial of \$2,904.77. The Pre-PBAC Response proposed increasing the rebate on the published AEMP per vial to [REDACTED] % for both the requested and existing blinatumomab listing for relapsed/refractory Ph- B-ALL provided repeat use of blinatumomab in the relapsed/refractory setting is permitted.
- 2.5 The requested restriction is narrower than the TGA indication as it includes specific clinical criteria, such as an ECOG performance status <2, the condition must not be present in the CNS or testes, and the level of MRD detected must be $\geq 10^{-4}$.
- 2.6 The level of MRD required to be detected to meet the eligibility criteria of initial therapy remains unchanged ($\geq 10^{-4}$ blasts), and is consistent with the level of MRD previously recommended by the PBAC (Blinatumomab PSD July 2018, para 7.3). Patients continuing therapy must be MRD negative ($< 10^{-4}$ blasts) and must achieve this response within two treatment cycles, consistent with the criterion previously recommended by the PBAC (Blinatumomab PSD July 2018, para 2.3). The PBAC previously recommended that the MRD level should be measured using PCR or flow cytometry (Blinatumomab PSD July 2018, para 7.3), however, the methodology and timing of MRD assessment remained undefined in the restriction proposed in the resubmission. The PBAC reiterated its previous consideration that the restriction should include a clinical criterion specifying that MRD must be measured using polymerase chain reaction or flow cytometry.
- 2.7 The resubmission requested the PBAC reconsider allowing more than one treatment with blinatumomab per patient between the requested MRD restriction and the existing blinatumomab relapsed/refractory listing, as the more restrictive approach may block patient access to blinatumomab when patient response to therapy suggests it may be the most effective clinical option in both settings. However, the commentary noted that limited evidence is available about repeat use of blinatumomab between the two settings. The ESC considered it may be clinically appropriate to allow repeat use of blinatumomab in the relapsed/refractory setting for patients who responded to treatment with blinatumomab in the MRD positive setting and remained relapse-free for a clinically meaningful period of time.
- 2.8 The ESC noted the criteria “the treatment must be the sole PBS-subsidised therapy for this condition” was proposed by the submission to specifically exclude concomitant use of blinatumomab and tyrosine kinase inhibitors (TKIs). The ESC considered that

concomitant use of blinatumomab and TKIs should not be excluded as treatment with TKIs are part of standard of care treatment for patients with Ph+ B-ALL. The ESC noted that though there were limited data for concomitant use in the MRD setting, clinical evidence in the relapsed/refractory setting (Sokolov et al., 2016; Sokolov et al., 2017; Assi et al., 2017) indicates that treatment with blinatumomab in combination with a TKI has a tolerable safety profile and is effective in patients with Ph+ B-ALL.

- 2.9 The ESC considered that the initial treatment restriction should include the criteria ‘Minimal residual disease must be measured using polymerase chain reaction or flow cytometry’, consistent with the PBAC’s previous advice that the methodology should be explicitly stated in the PBS restriction.
- 2.10 The PBAC previously noted that access to MRD testing is not consistently available throughout Australia (Blinatumomab PSD July 2018, para 2.13). The clinician survey conducted as part of the resubmission found that MRD testing is being funded through a number of mechanisms including by hospitals, the MBS, clinical trials, research funding donations and patient payment. The resubmission noted that MRD testing is not subsidised under the MBS and it was unclear which items physicians were using to claim MRD testing. While the PBAC noted that MRD testing is not MBS funded, it considered that it is routinely conducted in clinical practice.

For more detail on PBAC’s view, see section 7 PBAC outcome.

3 Background

Registration status

- 3.1 The approved TGA indications for blinatumomab are:
- The treatment of minimal residual disease (MRD) positive B-cell precursor acute lymphoblastic leukaemia (ALL) in patients in complete haematological remission; and
- The treatment of relapsed or refractory B-cell precursor acute lymphoblastic leukaemia.
- Note to indication: the indications in Philadelphia positive, MRD positive and paediatric patients were approved based on phase II, non-randomised evidence. An improvement in clinical outcomes by direct prospective comparison in a randomised setting relative to other standard-of-care salvage therapies has not been established.
- 3.2 Approval for the treatment of MRD positive disease in patients in complete haematological remission was granted on 7 May 2018, and at the same time, approval for the relapsed or refractory indication was extended to include Philadelphia chromosome positive patients.

Previous PBAC consideration

- 3.3 The outstanding matters of concerns from the previous July 2018 PBAC meeting are summarised in Table 2 below.

Table 2: Summary of key outstanding matters of concern (Blinatumomab PSD July 2018)

Matter of concern (July 2018 PSD [para])	How the resubmission addresses it
Restriction	
[2.3] The PBAC considered that a continuing restriction (written) would limit PBS-subsidised use of blinatumomab to patients who have responded to the drug after two cycles.	The resubmission requested discrete initial and continuing restrictions requiring demonstration of treatment response ($<10^{-4}$ blasts) to continue treatment.
[2.5; 7.3] The PBAC considered that patients achieving multiple remissions would be eligible for multiple courses of blinatumomab under the requested restriction, but no evidence for re-use of blinatumomab was presented. Blinatumomab should be limited to a once-in-a-lifetime treatment.	The resubmission requested the PBAC reconsider allowing more than one treatment with blinatumomab per patient between the requested MRD restriction and the existing blinatumomab relapsed/refractory listing.
[7.8] The PBAC considered that the level of MRD required for eligibility and the methodology of assessment should be explicitly stated in the PBS restriction.	The requested restriction includes the level of MRD required for eligibility ($\geq 10^{-4}$), but does not specify methodology of MRD testing.
[2.4] The ESC noted that data for paediatric, adolescent or Philadelphia chromosome positive patients was either absent or limited in the submission.	Applicability of the available clinical evidence to the broader eligible population discussed, and supporting expert evidence presented.
Clinical evidence	
[6.47] The PBAC noted that the population included in the propensity scoring analysis was likely to be significantly different to the eligible population in terms of age, Philadelphia chromosome status, remission history, MRD level and HSCT use, and this may affect survival gains associated with blinatumomab.	Applicability of the propensity score analysis to the eligible Australian population discussed in the resubmission.
[7.11] The PBAC noted the lack of applicability of the standard of care chemotherapy arm to Australian clinical practice.	Applicability of standard of care chemotherapy to Australian clinical practice discussed.
[7.11] The PBAC considered the ATE analysis was preferred to the ATT analysis given the ATT analysis had poorer matched covariates and a larger extent of data loss compared to the ATE analysis.	The resubmission presented a summary of the propensity score ATE and ATT analyses, but the economic analysis was informed by the ATE analysis.
[7.12] The PBAC considered the magnitude of any improvement in overall survival could not be determined due to the immaturity of the BLAST study data, confounding by HSCT use, the limitations and lack of applicability of the propensity score analysis, and the lack of statistically significant overall survival gain in the ATE analysis.	No additional comparative evidence was presented in the resubmission. Results of a clinician survey and expert opinion from the sponsor advisory board were presented to support the clinical evidence.
Economic model	
[6.60] The PBAC considered that the clinical evidence did not adequately support or reliably quantify an improvement in overall survival. The PBAC considered that the model was sensitive to the choice of analysis method, with the potentially less appropriate ATT method being used in the base case.	The resubmission modelled survival benefit using the ATE-weighted propensity score analysis in the base case and included results based on the ATT-weighted analysis as a sensitivity analysis. The base case assumes an overall survival advantage for blinatumomab over consolidation chemotherapy.
[6.60] The PBAC considered that the results of the modelled population (adult patients with B-ALL in first complete remission with $\text{MRD} \geq 10^{-3}$) may not be applicable to the broader proposed PBS population and the modelled circumstances of use may not be representative of Australian clinical practice.	The modelled population remained unchanged in the resubmission. However, sensitivity analyses were included to test the impact of patients populations with $\text{MRD} \geq 10^{-4}$ and patients in their 2 nd or 3 rd complete remission (higher baseline risk).

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Matter of concern (July 2018 PSD [para])	How the resubmission addresses it
[6.60] The PBAC considered that the modelled estimates may not be reliable given structural issues with the three-phase estimation of survival which required major adjustments to reconcile values as well as the lack of a time on treatment curve.	The resubmission estimated survival in the consolidation chemotherapy arm from Kaplan-Meier data for the ATE-weighted population of the historical control (0 to 4 years) with long term survival extrapolated using parametric survival functions (fitted to ATE-weighted survival data from 0-10 years from the historical control). The current model does not include a time on treatment curve but has made a series of crude adjustments to cost estimates to minimise logical inconsistencies.
[6.60] The PBAC considered that it was inappropriate to only include HSCT as a cost item and that HSCT should have been explicitly included as an event in the economic model. The PBAC acknowledged there may be limited data to inform assumptions relating to HSCTs, but considered inclusion was appropriate given HSCT was a treatment effect modifier (blinatumomab was not associated with any improvement in overall survival in patients undergoing HSCT) and is a major clinical event with discrete risks, benefits and costs.	The resubmission continued to exclude HSCT as an event in the model, and argued that including HSCT as an event would increase uncertainty given the limited data. The resubmission presented sensitivity analyses exploring the relative contribution of blinatumomab and HSCT to survival estimates.
[6.60] The PBAC considered the treatment, downstream management, salvage therapy and health state costs may not be reliable given substantial uncertainties with the sources and calculations of all costs.	The resubmission made the following revisions: consolidation chemotherapy based on a modified hyper-CVAD protocol; inclusion of a relative dose intensity factor to reflect treatment discontinuation in consolidation chemotherapy; inclusion of pre-medication and concomitant intrathecal prophylaxis costs for blinatumomab; updated health state (non-drug) costs using healthcare resource utilisation estimates from a sponsor-commissioned Australian physician survey.
[6.60] The PBAC noted that the overall EQ-5D results for the BLAST study were not provided and there was a lack of adequate documentation or validation to support utility values estimated through a complex multi-step approach.	The resubmission did not provide unadjusted EQ-5D results for the BLAST study. Additional documentation was provided for the approach used and validation of utility estimates.
[6.60] The PBAC considered that the costs in the blinatumomab arm were underestimated as hospitalisation costs were based on the minimum recommended hospitalisation from the product information rather than that reported in the BLAST study.	The resubmission introduced new cost items (intrathecal CSF prophylaxis, adverse events) and made other adjustments that resulted in a higher number of blinatumomab associated hospitalisations.
[6.60] The PBAC noted that the submission did not address the costs, accuracy and impacts of MRD testing.	The resubmission separately estimated MRD monitoring costs in the blinatumomab arm to assess treatment eligibility and response.
[6.60] The PBAC noted that the base case ICER of \$45,000-\$75,000, was high and significantly underestimated.	The base case ICER was \$75,000-\$105,000 (corrected during the evaluation).
Use of medicines	
[7.17] The PBAC considered the eligible population was underestimated in terms of incident ALL population, use of conditional four part multiplier, exclusion of patients with subsequent remissions and uptake of blinatumomab.	Uptake of blinatumomab in the eligible population increased.
[7.19] The PBAC considered that use of blinatumomab in the MRD setting may reduce or delay blinatumomab use in the existing relapsed/refractory listing, and that the impact of these reductions would need reductions in the risk sharing arrangement caps in the relapsed/refractory setting.	The resubmission acknowledged the need for an amended risk share arrangement, particularly if the PBAC approved more than one blinatumomab treatment between the MRD and relapsed/refractory settings.

Source: Constructed during the evaluation using Blinatumomab PSD July 2018.

Abbreviations: ATE, Average treatment effect; ATT, Average treatment effect of the treated; EQ-5D, EuroQoL- 5 dimension questionnaire; HSCT, Haematopoietic stem cell transplant; ICER, Incremental cost effectiveness ratio; MRD, minimal residual disease; Ph, Philadelphia chromosome; PSD, public summary document.

4 Population and disease

- 4.1 Acute lymphoblastic leukaemia (ALL) is a rare malignant disease of the bone marrow in which lymphoid precursor cells proliferate (approximately 1-1.5/100,000 of the general population). The incidence of ALL is highest in children under 5 years of age, declines slowly until the mid-20s and then begins to rise again slowly after 50 years of age. ALL may be related to either B-cell or T-cell precursors, with the majority of diagnoses identified as B-cell precursor ALL (B-ALL).
- 4.2 Relapse in B-ALL is believed to result from residual leukaemic blast cells persisting in haematological complete remission, at levels not detected in conventional morphologic assessments (<5% blast cells in bone marrow). The presence of residual leukaemic blast cells (in patients who have been assessed as having complete remission as assessed by conventional morphology analyses) is referred to as minimal residual disease (MRD) or molecular relapse.
- 4.3 More sensitive assays such as multicolour flow cytometry and polymerase chain reaction (PCR) provide detection of lower concentrations of MRD at levels of prognostic significance strongly correlated with risk of relapse. Different techniques have different sensitivities. Real-time quantitative PCR targeting immunoglobulin (Ig) can amplify a DNA or cDNA sequence unique to the leukemic clone cell resulting in assay sensitivity of 10^{-4} to 10^{-5} . Multicolour flow cytometry based on aberrant antigen expressions has an assay sensitivity of approximately 10^{-4} , or about 1 log less than PCR. While MRD assessment by multi-parametric flow cytometry and PCR are highly correlated, differences in methodology and sensitivity may influence results and therapeutic decisions (Berry et al. 2017).
- 4.4 At the July 2018 meeting, the PBAC considered that the MRD threshold of detection of $\geq 10^{-4}$ blasts proposed in the requested restriction is consistent with current clinical practice but was based on consensus (clinical opinion) rather than strong evidence. The Committee noted that as technology improves over time MRD may be detected at lower levels, but the clinical relevance of thresholds lower than 10^{-4} had not been established (Blinatumomab PSD July 2018, para 2.9-2.10).
- 4.5 The resubmission acknowledged that the definition of MRD is likely to change over time, but reiterated that the treatment effect of blinatumomab was not expected to vary with differing levels of sensitivity between the assay methodologies or MRD threshold of detection. The resubmission presented results from a sponsor-commissioned clinician survey, in which clinicians considered that if lower levels of MRD are left untreated they would be expected to increase within a short timeframe. The survey suggested variability in accepted MRD thresholds (10^{-2} to 10^{-5}) and schedule of MRD testing between clinicians and locations.

For more detail on PBAC's view, see section 7 PBAC outcome.

5 Comparator

- 5.1 The resubmission nominated standard of care consolidation chemotherapy as the main comparator (unchanged from the previous submission). At the July 2018 meeting the PBAC accepted that blinatumomab may be used in a number of discrete therapeutic roles including as a primary treatment, disease suppression until HSCT (bridge to transplant), optimisation of HSCT (by eliminating MRD) and treatment of molecular relapse and considered that standard of care chemotherapy was the appropriate comparator in all these settings (Blinatumomab PSD July 2018, para 5.4-5.5; 7.9).

6 Consideration of the evidence

Sponsor hearing

- 6.1 There was no hearing for this item.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from individuals (5), health care professionals (14) and organisations (3) via the Consumer Comments facility on the PBS website. The comments described benefits of treatment with blinatumomab as a bridge to HSCT and its tolerable safety profile. The comments also emphasised the lack of therapies in the MRD positive setting and indicated that blinatumomab is an important treatment option in this setting.
- 6.3 The correspondence from the Australian Leukaemia and Lymphoma Group (ALLG) and Haematology Society of Australia and New Zealand (HSANZ) indicated support for subsidised access to blinatumomab, noting the poor prognosis and high risk of relapse in patients with MRD positive disease. The ALLG and HSANZ considered that the best outcome for patients would be to receive blinatumomab at the time of first molecular failure, rather than waiting for eventual clinical relapse. Further, the correspondence noted that blinatumomab was now being incorporated into many protocols internationally for the treatment of MRD positive disease.
- 6.4 Rare Cancers Australia highlighted the psychological impact of disease on patients and indicated that availability of blinatumomab in this setting would have a positive impact on the psychological wellbeing of patients in terms of allaying fears of disease relapse and progression.
- 6.5 The Leukaemia Foundation emphasised the poorer prognosis of B-ALL in adult patients compared to that of children who represent the majority of cases and the importance of achieving MRD negative status in terms of improving survival and suitability for HSCT. The Leukaemia Foundation also noted the many personal positive responses received from patients with ALL who had received treatment with blinatumomab in relation to improvement in quality of life, mental health and reduced side effects.

Clinical trials

- 6.6 No new clinical evidence relevant to the MRD setting was provided in the resubmission. The resubmission noted that ongoing randomised controlled phase III trials of blinatumomab in this patient population mentioned at the sponsor hearing at the July 2018 PBAC meeting have been amended to single arm studies, and are not yet completed. No additional information was available during the evaluation.
- 6.7 One additional ongoing phase 3 study in children and adolescents with chemotherapy resistant B-ALL (NCT03643276; estimated completion July 14 2028) and one additional phase 2 study in the MRD setting (NCT03523429; estimated completion January 2025) were identified in the literature search. Six ongoing studies identified in the July 2018 submission remain ongoing. The ESC noted that the submission advised that these trials have been amended to a single arm design because the use of chemotherapy in this patient group was deemed unethical due to known lack of effect.
- 6.8 The resubmission was based on the same clinical evidence presented at the July 2018 meeting; i.e. a propensity score indirect analysis of one single arm blinatumomab study (BLAST; N=116) and one retrospective historical control cohort study of patients receiving treatment with standard of care chemotherapy (Study 20120148; N=287) in patients with B-ALL in haematological remission with MRD.
- 6.9 The results of a sponsor-commissioned online survey of Australian clinicians with experience treating patients with ALL were presented as supportive evidence, in conjunction with advice from an expert advisory committee to the sponsor. The clinician survey was small (520 haematologists were invited to participate, however the survey was closed after 25 questionnaires were completed), included only three clinicians with paediatric experience, and may not be representative.
- 6.10 Details of the studies presented in the submission are provided in the table below.

Table 3: Studies and associated reports presented in the submission

Study ID	Protocol title/ Publication title	Publication citation
Key single arm study		
BLAST (MT103-203) NCT01207388	<p>A confirmatory multicenter, single-arm study to assess the efficacy, safety, and tolerability of the BiTE® antibody blinatumomab in adult subjects with minimal residual disease (MRD) of B-precursor acute lymphoblastic leukemia.</p> <p>Gökbuget, N., et al. Blinatumomab for minimal residual disease in adults with B-precursor acute lymphoblastic leukemia.</p> <p>Gökbuget, N., et al. Long-term outcomes after blinatumomab treatment: Follow-up of a phase 2 study in patients (PTS) with minimal residual disease (MRD) positive b-cell precursor acute lymphoblastic leukemia (ALL).</p> <p>Gökbuget, N., et al. BLAST: A confirmatory, single-arm, phase 2 study of blinatumomab, a bispecific T-cell engager (BiTE®) antibody construct, in patients with minimal residual disease B-precursor acute lymphoblastic leukemia (ALL).</p>	<p>Report date: 24 September 2014.</p> <p><i>Blood First Edition Paper</i>, online January 22, 2018.</p> <p><i>Blood</i> 2015; 126(23): 680.</p> <p><i>Blood</i> 2014; 124(21): 379.</p>
Supportive single arm study		
MT103-202 NCT00560794	<p>An open-label, multicenter phase 2 study to investigate the efficacy, safety, and tolerability of the Bi-specific T-cell engager (BiTE®) MT103 in patients with minimal residual disease (MRD) of positive B-precursor acute lymphoblastic leukemia (ALL).</p> <p>Topp, M. S., et al. Long-term follow-up of hematologic relapse-free survival in a phase 2 study of blinatumomab in patients with MRD in B-lineage ALL.</p> <p>Klinger, M., et al. Immunopharmacologic response of patients with B-lineage acute lymphoblastic leukemia to continuous infusion of T cell-engaging CD19/CD3-bispecific BiTE antibody blinatumomab.</p> <p>Topp, M. S., et al. Targeted therapy with the T-cell - Engaging antibody blinatumomab of chemotherapy-refractory minimal residual disease in B-lineage acute lymphoblastic leukemia patients results in high response rate and prolonged leukemia-free survival.</p>	<p>Report date: 7 November 2013.</p> <p><i>Blood</i> 2012; 120(26): 5185-5187.</p> <p><i>Blood</i> 2012; 119(26): 6226-6233.</p> <p><i>Journal of Clinical Oncology</i> 2011; 29(18): 2493-2498.</p>
Supportive single arm study		
20120148 (NCT02010931)	<p>A retrospective analysis of haematological relapse free survival and overall survival in adult patients with Philadelphia-negative B-precursor acute lymphoblastic leukemia in complete haematological remission with minimal residual disease.</p> <p>Propensity score analysis of relapse free survival and overall survival among adult patients with minimal residual disease (MRD) in study 20120148.</p>	<p>Report date: 12 December 2014.</p> <p>Report date: 30 January 2017 (updated 19 February 2018).</p>

Source: Tables 21 and 22, pp.27-29 of the July 2018 submission.

Abbreviations: ALL, acute lymphoblastic leukaemia; MRD, minimal residual disease.

6.11 The key features of the studies are unchanged from the previous submission and are summarised in the table below.

Table 4: Key features of the included evidence

Study	N	Design	Risk of bias	Intervention	Patient population	Outcome	Use in model
BLAST	116	Phase II, open label, multicentre, single arm	High	Blinatumomab IV 15 mcg/m ² /day (4 wks), Treatment free (2 wks), Up to 4 cycles.	B-ALL ≥18 years, haematological complete remission, MRD ≥10 ⁻³ in an assay with minimum sensitivity of 10 ⁻⁴ by PCR or flow cytometry, ECOG performance status ≤1.	MRD response rate, haematological RFS at 18 months, overall survival from first blinatumomab dose, 100-day mortality after alloHSCT; EQ-5D, EORTC-QLQ-C30	Propensity score-adjusted hazard ratios (ATE and ATT).
MT103-202	21	Phase II, exploratory, open label, multicentre, single arm	High	Blinatumomab IV 15 mcg/m ² /day (4 weeks), Treatment free (2 weeks), Increased to 30 ug/m ² /day if no response cycle 1, increased for all non-responders cycle 2.	B-ALL ≥18 years, Haematological complete remission, MRD ≥10 ⁻⁴ in an assay with minimum sensitivity of 10 ⁻⁴ by PCR, ECOG performance status ≤1.	MRD response rate, haematological RFS, MRD progression.	Not used
20120148	287	Retrospective historical cohort	High	Non-interventional, Standard-of-care treatment as per site study protocols.	Ph- B-ALL ≥15 years, Haematological complete remission, MRD ≥10 ⁻⁴ by PCR or ≥10 ⁻³ by flow cytometry.	Haematological RFS, overall survival from MRD detection, 100-day mortality after alloHSCT,	Propensity score-adjusted survival curve (ATT and ATE)

Source: Table 23, p.31 of the of the July 2018 submission.

Abbreviations: alloHSCT, allogeneic haematopoietic stem cell transplantation; ATE, average treatment effects; ATT, average treatment effect of the treated weights; B-ALL, B-cell precursor acute lymphoblastic leukaemia; ECOG, Eastern Cooperative Oncology Group; EQ-5D, EuroQoL- 5 dimension questionnaire; MRD, minimal residual disease; Ph-, Philadelphia chromosome negative; PCR, Polymerase chain reaction; RFS, relapse free survival.

Applicability issues

- 6.12 At the July 2018 meeting the PBAC considered that the propensity score adjustments led to better matching of known patient characteristics but may have reduced the applicability of results to the broader target population, as it excluded patients with Philadelphia chromosome positive B-ALL, subsequent complete remissions, or a smaller extent of minimal residual disease (MRD ≥10⁻⁴ to <10⁻³), who would be eligible for blinatumomab under the proposed PBS restriction (Blinatumomab PSD July 2018, para 6.34).
- 6.13 No evidence was presented supporting the use of blinatumomab in children, despite the submission assuming that around 37% of the treated population would be children. The resubmission acknowledged age is a prognostic factor, but noted that the PBAC previously recommended blinatumomab for use in children in the relapsed/refractory setting based on a similar level of evidence and absence of available comparative data. At the July 2018 meeting, the PBAC considered that the

appropriate eligible population should include patients of any age (i.e. including children and adolescents) (Blinatumomab PSD July 2018, para 7.3).

- 6.14 The resubmission stated that while tyrosine kinase inhibitors have greatly improved the prognosis of Philadelphia chromosome positive patients, the applicability of results from the Philadelphia chromosome negative population remains uncertain. However, the resubmission argued that the impact is likely to be small given Philadelphia chromosome positive patients represent a small subgroup of the disease (20-30% adults; 5% children).
- 6.15 The resubmission agreed with PBAC's previous consideration that blinatumomab may be more effective in the first complete remission setting than in later remissions, but that, over time, blinatumomab would predominantly be used in first complete remission (Blinatumomab PSD July 2018, para 2.6).
- 6.16 The resubmission acknowledged the high rate of HSCT observed in the BLAST study (72.6%) compared to the historical control (38.5%) may have been due to a more aggressive approach to HSCT, high rates of HSCT in older patients or offering HSCT with mismatched donors. The sponsor's advisory board claimed that the transplant rate from the TOWER trial in the relapsed/refractory setting would be more representative of clinical practice (standard of care 23.9%; blinatumomab 24.7%). The advisory board also suggested that blinatumomab treatment of MRD may lead to a reduced number of HSCTs as some patients would decline to undergo transplantation following successful treatment with blinatumomab. On the other hand, blinatumomab may act as a bridge to transplant in some patients. Overall, the difference in transplant rates makes it difficult to ascertain likely survival outcomes in clinical practice with blinatumomab treatment.
- 6.17 The ESC considered that the high rate of HSCT observed in the BLAST study was reflective of the younger age of patients in BLAST and considered that the transplant rate from the TOWER trial would be more representative of the transplant rate in adult patients in clinical practice. The ESC disagreed with the submission's claim that blinatumomab treatment would lead to a reduced number of HSCTs in adult patients, noting there is currently no evidence that achieving MRD negative status would translate to a cure. The ESC considered that in clinical practice, blinatumomab would be used as a bridge to transplant in suitable patients given MRD positive patients are designated as high risk and current clinical consensus is that HSCT provides the best chance of cure for this population.
- 6.18 The resubmission acknowledged that there was limited information about the standard of care chemotherapies used in Study 201210148 (historical cohort), and that the chemotherapy regimens used were more than 10 years old. The resubmission noted that patients in the historical control study received various intensive standard or investigational chemotherapy regimens according to adult protocols. The most common protocol used in the historical control study was GMALL (German multicentre study group or adult ALL), while the resubmission stated that hyper-CVAD treatment protocol is the most common protocol in current Australian clinical practice

(based on feedback from Australian clinicians). The ESC considered that, while the chemotherapy backbones used in the historical control arms were unlikely to differ significantly to those used in current practice, there have been improvements in supportive care and disease management since the historical control (wherein most patients were treated between 2000 and 2010). Overall, the ESC considered that this may have confounded the comparison as differences in supportive care and disease management may account for some of the differences in outcomes observed between BLAST and the historical control study.

Comparative effectiveness

6.19 The resubmission relied on the results of the propensity score weighted indirect analysis for the average treatment effect (ATE) and average treatment effect of the treated (ATT) populations previously considered by the PBAC at the July 2018 meeting. The primary propensity score-based weight used was ATE with the analysis using ATT presented as a sensitivity analysis. The ESC considered that while the ATE analysis resulted in better-matched covariates and a smaller extent of data loss compared to the ATT method used in the July 2018 submission, the applicability of the propensity matched population to the Australian population remained an outstanding issue. The ESC maintained that the propensity-matched population would likely differ to the Australian PBS population as the propensity score analysis excluded Ph+ patients, excluded children, excluded patients with a smaller extent of MRD positive disease and had a high rate of HSCT.

6.20 Table 5 and Figure 1 summarise the propensity score weighted indirect comparison of blinatumomab and standard of care chemotherapy for relapse free survival (ATE and ATT analyses).

Table 5: Relapse free survival (RFS) propensity scoring analysis (ATE and ATT; PAS; stabilised IPTW)

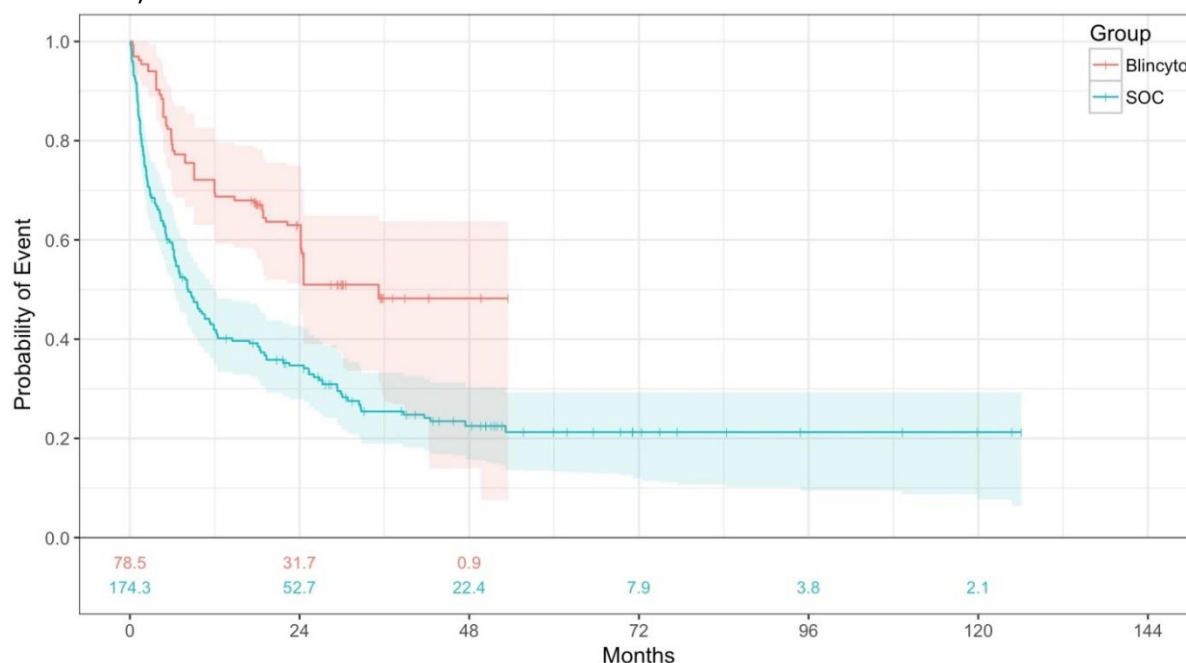
	ATE analysis		ATT analysis	
	Blinatumomab (N=78.5)	Historical control (N=174.3)	Blinatumomab (N=20.9)	Historical control (N=44.4)
Stabilised IPTW Kaplan-Meier estimates (not adjusted for alloHSCT)				
18 months (95% CI)	0.67 (0.58, 0.78)	0.39 (0.33, 0.48)	0.64 (0.54, 0.76)	0.33 (0.26, 0.42)
RFS median months (95% CI)	35.2 mths (24.2, NE)	8.3 mths (6.2, 11.8)	35.2 mths (6.3, NE)	6.5 mths (2.9, 11.4)
Stabilised IPTW				
	Hazard ratio (95% CI)^a		Hazard ratio (95% CI)^a	
not adjusted for alloHSCT	0.47 (0.30, 0.73)		0.42 (0.29, 0.60)	
adjusted for alloHSCT	0.50 (0.32, 0.78)		0.45 (0.31, 0.65)	

Source: Table 21, p.66 of the resubmission; Tables 2.6.15, p.73, and 2.6.14, p.142 of the July 2018 commentary.

Abbreviations: alloHSCT, allogeneic haematopoietic stem cell transplantation; ATE, average treatment effect; ATT, average treatment effect of the treated; CI, confidence interval; IPTW, inverse probability of treatment weight; NE, not evaluable; PAS, primary analysis set; RFS, relapse free survival.

^a Results <1 favour blinatumomab. Statistically significant comparative results in bold.

Figure 1: Kaplan-Meier relapse-free survival with blinatumomab and consolidation chemotherapy (ATE-weighted survival data)



Source: Figure 26, p.132 of the resubmission

6.21 In the primary ATE analysis, blinatumomab showed a statistically significant increase in median relapse free survival of 26.9 months compared with standard of care chemotherapy (not adjusted for alloHSCT). Similar results were reported for the exploratory ATT analysis; median relapse free survival of 28.7 months (not adjusted for alloHSCT). The ESC noted the plateau in the relapse-free survival curve of the standard of care chemotherapy arm after 48 months. The ESC noted this was consistent with the clinical course of B-ALL in that the majority of relapses occur in the first few years following treatment.

6.22 Table 6 and Figure 2 summarise the results of the propensity score weighted indirect comparison of blinatumomab and standard of care chemotherapy in overall survival (ATE and ATT analyses), presented at the July 2018 meeting.

Table 6: Overall survival (OS) propensity scoring analysis (ATE and ATT; PAS; stabilised IPTW)

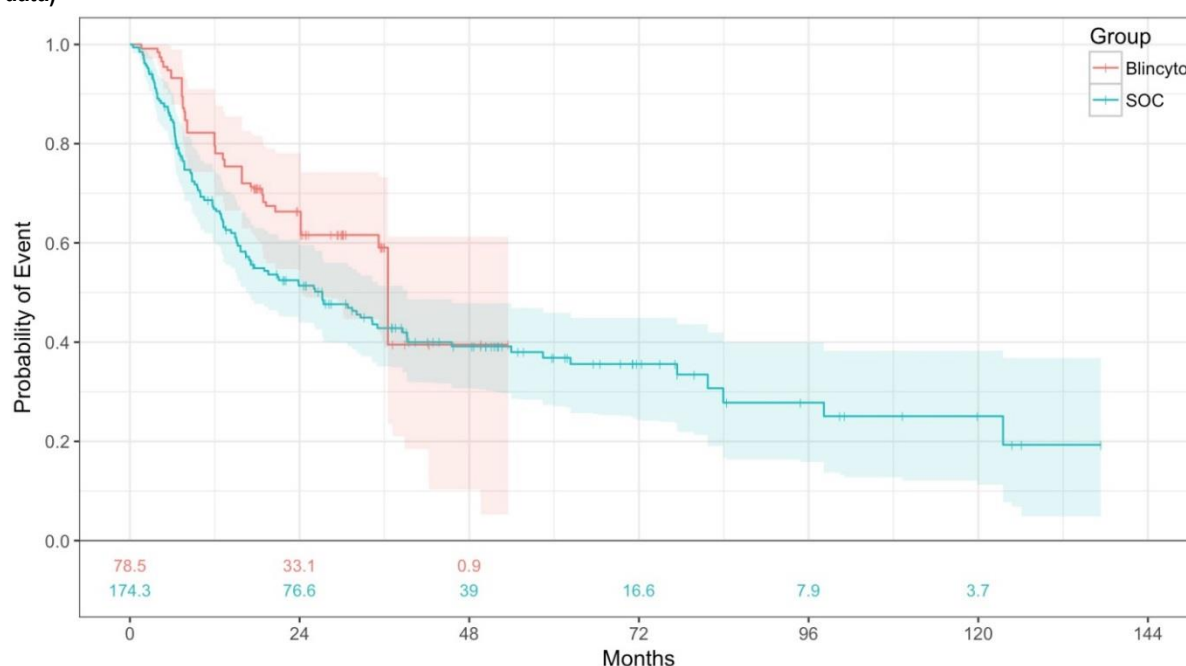
	ATE analysis		ATT	
	Blinatumomab (N=78.5)	Historical control (N=174.3)	Blinatumomab (N=20.9)	Historical control (N=44.4)
Stabilised IPTW Kaplan-Meier estimates (not adjusted for alloHSCT)				
18 months (95% CI)	0.71 (0.62, 0.81)	0.55 (0.48, 0.63)	0.71 (0.62, 0.82)	0.51 (0.42, 0.62)
OS median months (95% CI)	36.5 mths (24.2, NE)	27.2 mths (16.4, 38.6)	NR (15.8, NE)	19.6 mths (11.7, 45.5)
Stabilised IPTW				
	Hazard ratio (95% CI)^a		Hazard ratio (95% CI)^a	
not adjusted for alloHSCT	0.68 (0.42, 1.09)		0.58 (0.37, 0.91)	
adjusted for alloHSCT	0.76 (0.47, 1.24)		0.63 (0.41, 0.98)	

Source: Table 21, p.66 of the resubmission; Tables 2.6.16, p.141 and 2.6.17, p.142 of the July 2018 commentary.

Abbreviations: alloHSCT, allogeneic haematopoietic stem cell transplantation; ATE, average treatment effect; ATT, average treatment effect of the treated; CI, confidence interval; IPTW, inverse probability of treatment weight; NE, not evaluable; NR, not reached; OS, overall survival PAS, primary analysis set.

^a Results <1 favour blinatumomab. Statistically significant comparative results in bold.

Figure 2: Kaplan-Meier overall survival with blinatumomab and consolidation chemotherapy (ATE-weighted survival data)



Source: Figure 27, p.132 of the resubmission

6.23 In the primary ATE analysis blinatumomab showed no statistically significant difference in overall survival compared to standard of care chemotherapy (hazard ratio 0.68; 95% CI 0.42, 1.09). However, results from the exploratory ATT analysis showed a statistically significant increase in overall survival (median not reached for blinatumomab vs 19.6 months for standard of care chemotherapy; HR 0.58; 95% CI 0.37, 0.91; not adjusted for alloHSCT).

6.24 Table 7 summarises the impact of haematopoietic stem cell transplant (HSCT) on overall survival using a Cox proportional hazards model with an interaction term for treatment and the time-dependent HSCT covariate.

Table 7: Treatment effect / time dependent HSCT covariate interaction for overall survival (ATE stabilised IPTW)

	HSCT status	Hazard ratio (95% CI) ^a
	Blinatumomab vs control	No HSCT
	After HSCT	1.033 (0.611, 1.748)

Source: Table 10-1, p.50 of the 203-148 MRD Propensity Score Analysis Report: Feb18.

Abbreviations: HSCT, haematopoietic stem cell transplantation; CI, confidence interval; IPTW, inverse probability of treatment weight.

^a Results <1 favour blinatumomab. Statistically significant results in bold.

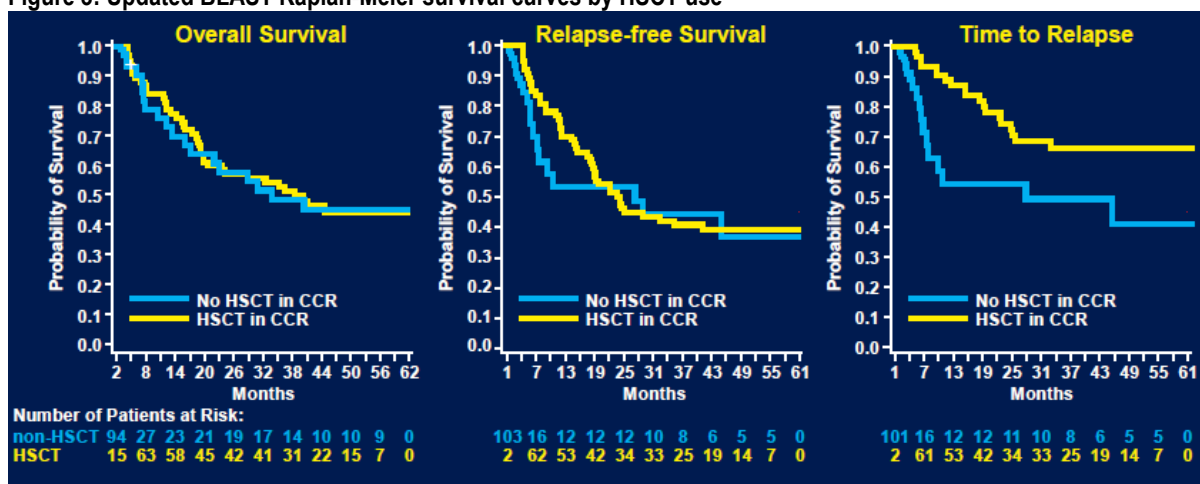
Note that patient numbers/weights for this analysis were not provided in the propensity score analysis report

6.25 Blinatumomab was associated with a statistically significant improvement in overall survival prior to or in the absence of HSCT, but there was no difference in overall survival following HSCT.

6.26 The ESC noted that updated survival data from BLAST (Goekbuget et al., 2018) provided with the Pre-Sub-Committee Response (PSCR) indicated that overall survival across patients in continuous complete remission were generally similar regardless of whether or not patients received HSCT (Figure 3). The ESC noted that, at the time of

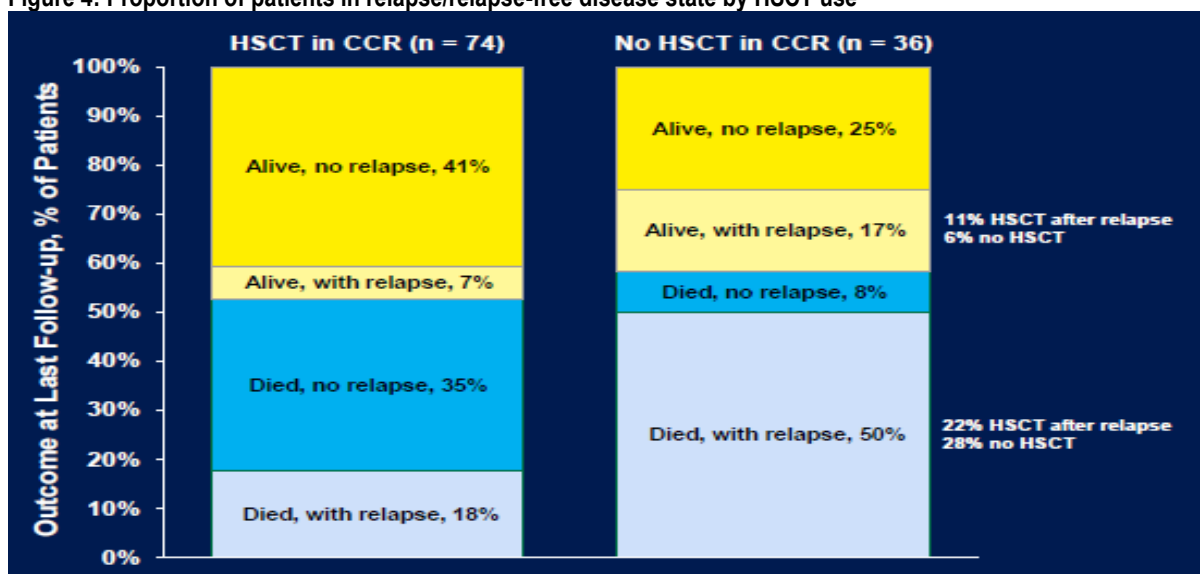
the data-cut, mortality in patients who did not undergo HSCT was largely due to relapse, while mortality in patients who underwent HSCT was mainly in un-relapsed patients and likely due to HSCT complications (Figure 4). The ESC considered that deaths due to HSCT complications would likely occur in the first few years post-HSCT, and thus a difference in overall survival with HSCT versus without HSCT may become apparent over time (with future data-cuts) given current clinical consensus is that HSCT provides the best chance of cure for this population. The ESC noted that the majority of patients who underwent HSCT in continuous complete remission remained relapse free.

Figure 3: Updated BLAST Kaplan-Meier survival curves by HSCT use



Source: Goekbuget et al., 2018 presentation at the American Society of Haematology (ASH) 2018 Annual Meeting provided with the PSCR

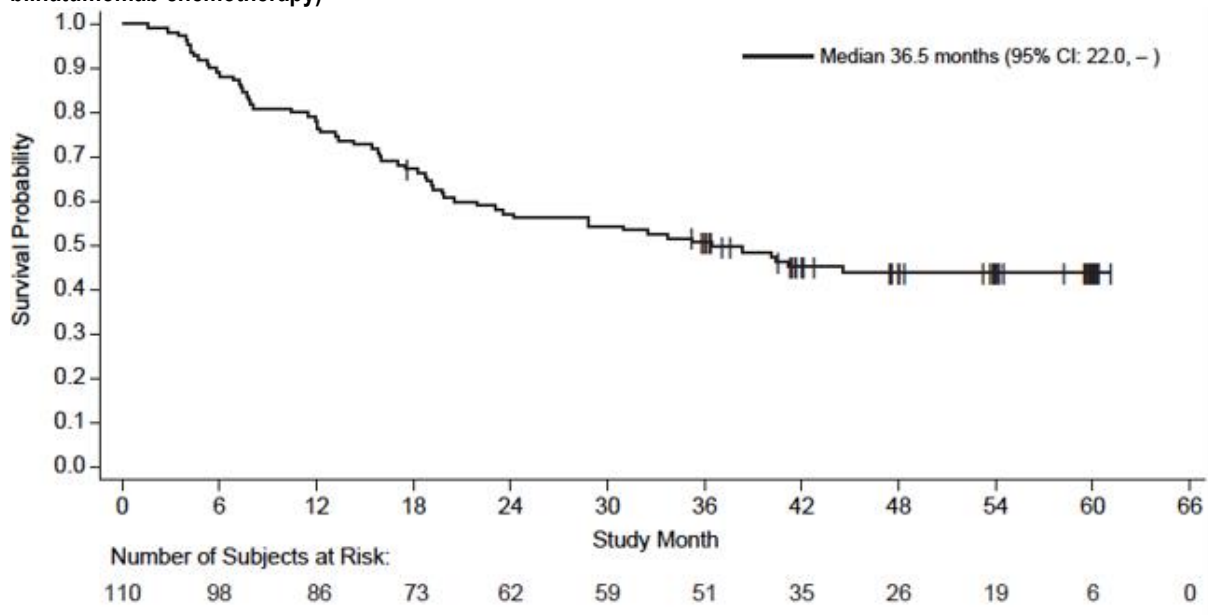
Figure 4: Proportion of patients in relapse/relapse-free disease state by HSCT use



Source: Goekbuget et al., 2018 presentation at the American Society of Haematology (ASH) 2018 Annual Meeting provided with the PSCR

- 6.27 The PBAC considered that MRD positive patients treated with blinatumomab would follow one of the below simplified pathways:
- MRD negative -> HSCT -> survival (potential for cure)
 - MRD negative -> HSCT -> death from relapse or HSCT complications
 - MRD negative -> no HSCT -> survival (potential for cure)
 - MRD negative -> no HSCT -> death from relapse
 - MRD positive -> HSCT -> survival (potential for cure)
 - MRD positive -> HSCT -> death from relapse or HSCT complications
 - MRD positive -> no HSCT -> survival (potential for cure)
 - MRD positive -> no HSCT -> death from relapse.
- 6.28 The PBAC considered that in some pathways it was unclear whether the patient outcome would be attributable to either blinatumomab or HSCT, while in other pathways the outcome may be fully attributable to either a single course or multiple courses of blinatumomab. The PBAC also considered that treatment with blinatumomab may not effect long-term outcomes in some patients who may relapse regardless of treatment.
- 6.29 At the July 2018 meeting, the PBAC considered that the claim of superior comparative effectiveness was adequately supported by the data, although the magnitude of the incremental effectiveness was uncertain. The Committee considered that the clinical evidence did not adequately support or reliably quantify an improvement in overall survival compared to consolidation chemotherapy (Blinatumomab PSD July 2018, para 6.47).
- 6.30 The PSCR presented updated overall survival data from the single-arm BLAST study (Figure 3). The ESC considered these data were informative because the PBAC previously considered the BLAST data were immature in the context of claiming an overall survival advantage (Blinatumomab PSD July 2018, para 7.12).

Figure 5: Updated BLAST Kaplan-Meier curve for overall survival (FAS, not censored at alloHSCT or post-blinatumomab chemotherapy)



Source: Goekbuget et al., 2018 abstract provided with PSCR

Abbreviations: alloHSCT, allogeneic haematopoietic stem cell transplantation; FAS, full analysis set.

- 6.31 From the updated data, median overall survival was 36.5 months (95% CI 22.0, not estimable) with a median follow up of 4.5 years (53.1 months). The ESC noted that the overall survival curve indicates a plateau after 48 months; however, given the small number of patients remaining at risk in this part of the curve, the ESC considered the data were still immature and it was uncertain whether the observed plateau would translate to a long-term survival benefit in the remaining patients. The ESC considered that more mature data from the BLAST study in the future would be informative in determining the durability of survival.
- 6.32 The ESC noted that the updated data from the single-arm BLAST study were not included in the comparative analysis (i.e. the propensity score weighted indirect analysis for the ATE and ATT). The ESC considered that the magnitude of benefit compared with standard of care chemotherapy remains uncertain and that it would be informative for the updated data to be included in the comparative analysis. The Pre-PBAC Response did not provide a revised comparative analysis incorporating updated survival data from the BLAST trial and contended that given the consistency with earlier data, incorporating the updated survival data would be unlikely to change the results.

Comparative harms

6.33 No new clinical safety data were presented in addition to that considered by the PBAC at the July 2018 meeting. Table 8 summarises the key treatment emergent adverse events for blinatumomab in the BLAST and MT103-202 studies in the MRD setting and comparative safety in the TOWER study in the relapsed/refractory setting. As with the previous submission, no safety data were presented for standard of care chemotherapy in the MRD setting.

Table 8: Comparison of key treatment related adverse events

	MT103-202	BLAST	TOWER (relapsed/refractory setting)			
	Blinatumomab (N=21)	Blinatumomab (N=116)	Blinatumomab (N=267)	SOC (N=109)	Blinatumomab vs SOC	
					Odds ratio ^a (95% CI)	Risk difference ^b (95% CI)
Treatment-related adverse event n (%)						
Any adverse event	21/21 (100%)	112 (96.6%)	214 (80.2%)	92 (84.4%)	0.75 (0.41, 1.36)	-0.04 (-0.13, 0.04)
SAE	9/21 (42.9%)	60 (51.7%)	76 (28.5%)	34 (31.2%)	0.88 (0.54, 1.43)	-0.03 (-0.13, 0.08)
Grade ≥3	13/21 (61.9%)	60 (51.7%)	144 (53.9%)	78 (71.6%)	0.47 (0.29, 0.75)	-0.18 (-0.28, -0.07)
Grade ≥4	6/21 (28.6%)	26 (22.4%)	59 (22.1%)	51 (46.8%)	0.32 (0.20, 0.52)	-0.25 (-0.35, -0.14)
Fatal AE within 30 days of treatment	0/21	1 (0.9%)	8 (3.00%)	8 (7.3%)	0.39 (0.14, 1.07)	-0.04 (-0.10, 0.01)

Source: Table 22, p.70 of the resubmission.

Abbreviations: AE, adverse event; MRD, minimal residual disease; R/R, relapse refractory; SAE, serious adverse events; SOC, standard of care chemotherapy.

^a Results <1 favours blinatumomab. ^b Results <0 favours blinatumomab. Statistically significant result in bold.

6.34 Treatment emergent adverse events were reported in 97% of patients in the BLAST study, with a substantial proportion of patients reporting serious treatment emergent adverse events (51.7%), Grade ≥3 events (51.7%) and Grade ≥4 events (22.4%). The most frequently reported adverse events were pyrexia, headache, tremor, chills and fatigue. The most frequently reported Grade ≥3 events were neutropenia (13%) and pyrexia (7%).

6.35 Important risks associated with blinatumomab identified in the expanded assessment of harms include neurologic events, infections, cytokine release syndrome, infusion reactions, tumour lysis syndrome, capillary leak syndrome, elevated liver enzymes, medication errors, febrile neutropenia and neutropenia and decreased immunoglobulin. The blinatumomab product information includes a boxed warning regarding cytokine release syndrome and neurological toxicities, which may be severe, life threatening, or fatal, and reactivation of JC viral infection.

6.36 At the July 2018 meeting the PBAC considered that the comparative safety outcomes from the relapsed/refractory setting are unlikely to reflect circumstances of use in the MRD population (longer blinatumomab treatment length, less fit patients, more aggressive chemotherapy regimens) and that safety data for the intended population would have been more informative (Blinatumomab PSD July 2018 para 7.13). The PBAC considered that blinatumomab and standard of care chemotherapy have different safety profiles, with both therapies being associated with potentially life-threatening complications (Blinatumomab PSD July 2018, para 7.14). Overall, the

PBAC considered the claim of non-inferior safety was not adequately supported by the data (Blinatumomab PSD July 2018, para 6.50).

Benefits/harms

- 6.37 The benefits and harms presented in the resubmission are unchanged from the July 2018 submission.
- 6.38 Based on indirect evidence presented in the submission in the ATE propensity score analysis, treatment with blinatumomab was associated with an increase in median relapse free survival of 26.9 months and no difference in overall survival compared with standard of care chemotherapy.
- 6.39 No data were presented in the submission comparing adverse events associated with blinatumomab and standard of care chemotherapy in the MRD positive population.

Clinical claim

- 6.40 The clinical claim in the resubmission was unchanged from the July 2018 submission.
- 6.41 The resubmission described blinatumomab as superior in terms of effectiveness compared with standard of care chemotherapy (post induction *consolidation*) and non-inferior in terms of safety, in the treatment of B-ALL in haematological complete remission with minimal residual disease.
- 6.42 The ESC considered that although the therapeutic conclusion presented in the resubmission is supported by the evidence presented, the extent of benefit remains uncertain for the following reasons:
- While updated clinical evidence from the single-arm BLAST study provides a clearer indication that blinatumomab may be associated with an overall survival advantage, the data remain immature in the context of determining whether blinatumomab will lead to long-term gains in overall survival.
 - The ESC noted that no new comparative evidence was provided and recalled that the PBAC had previously considered that the clinical evidence did not adequately support an improvement in overall survival for patients treated with blinatumomab compared to those treated with standard of care chemotherapy, or adequately quantify the magnitude of benefit demonstrated in relapsed free survival (Blinatumomab PSD July 2018 para 6.47). The ESC considered that the magnitude of the incremental benefit remains uncertain and it would be informative for the updated OS data to be included in the comparative analysis (i.e. the ATE propensity score analysis).
 - The resubmission did not adequately address the issues of concern raised by the PBAC at the July 2018 meeting (i.e. the high risk of bias in the propensity score analysis, the potential of confounding variables not accounted for, substantial data loss due to adjustments to improve between study comparability (particularly in the ATT analysis) and the applicability of the matched population remaining in the propensity score analysis to the proposed Australian population).

It also remains unclear whether the results of the standard care arm are applicable to Australian clinical practice, given the age of the study (most patients were treated between 2000 and 2010, and there have been improvements in supportive care since this time).

- No comparative adverse event data for the MRD setting were provided in the resubmission. At the July 2018 meeting, the PBAC considered that the clinical evidence did not adequately support the claim that blinatumomab is non-inferior to standard of care chemotherapy in the MRD setting.
- The ESC considered that the claim of non-inferior comparative safety was not adequately supported by the data.

6.43 The PBAC reiterated its previous consideration that blinatumomab is effective in eliminating MRD and is associated with durable relapse-free survival. As such, the PBAC considered that the claim of superior comparative effectiveness was adequately supported by the data.

6.44 The PBAC considered that the claim of non-inferior comparative safety was not adequately supported by the data.

Economic analysis

6.45 The resubmission presented a stepped economic evaluation of blinatumomab compared to consolidation chemotherapy for the treatment of patients with B-ALL in complete remission with minimal residual disease.

6.46 Key components of the model are summarised in the table below.

Table 9: Key components of the economic evaluation

Component	Description
Type of analysis	Cost-effectiveness analysis/cost-utility analysis
Outcomes	Relapse-free life years; life years; quality-adjusted life years
Time horizon	30 years
Methods used to generate results	Partitioned survival analysis
Treatments	Blinatumomab, consolidation chemotherapy
Health states	Relapse-free disease, relapsed disease, death
Cycle length	3 months (with half cycle corrections)
Transition probability	<p>Kaplan-Meier curves for relapse-free survival and overall survival from 0 to 4 years for consolidation chemotherapy based on the ATE-weighted propensity score analysis population from the historical control (Study 20120148).</p> <p>Standard parametric curves for relapse-free and overall survival fitted using 10-year Kaplan-Meier data for consolidation chemotherapy based on the ATE-weighted propensity score analysis population from the historical control (Study 20120148). Extrapolation using log-normal distribution used in the base case for both relapse-free and overall survival.</p> <p>Survival curves for relapse-free survival and overall survival were calculated from 0 to 4 years for blinatumomab based on the estimated hazard ratio from the propensity score analysis using ATE weights. Relapse-free survival and overall survival beyond 4 years were extrapolated based on the assumption of no difference in hazards between treatments</p>
Discount rate	5% for costs and outcomes, applied annually
Software package	Excel 2013

Source: Table 66, p.123 of the submission

Abbreviations: ATE, average treatment effect

6.47 Key drivers of the economic model are summarised in the table below.

Table 10: Key drivers of the model

Description	Method/Value	Impact
Blinatumomab overall survival benefit	The resubmission modelled an overall survival improvement with blinatumomab compared to consolidation chemotherapy based on the ATE-weighted analysis (HR 0.68; 95% CI 0.42, 1.09), which did not include the updated BLAST study data. The ESC noted that, in the comparative analysis provided in the submission, the improvement in OS was not statistically significant and further considered that the results may not be reliable given the results may be confounded by historical control data (informing the standard of care chemotherapy arm) which may not reflect outcomes current Australian practice.	High, favours blinatumomab
Impact of HSCT	<p>The model did not include HSCT as an event. The resubmission provided hypothetical scenarios exploring the relative contribution of blinatumomab and HSCT to survival estimates based on a post hoc retrospective analysis (Dhedin et al 2015) which indicated that HSCT provided no additional benefit to patients who were MRD- post-induction. The relevance of the Dhedin (2015) analyses to the BLAST study was unclear due to population differences and unclear generalisability of results to patients who become MRD negative through the use of post-induction therapies.</p> <p>The results of the hypothetical scenarios are uninformative as the adjustments for HSCT effects were applied to the population as a whole and therefore do not adequately account for the discrete subgroup populations who undergo HSCT or do not proceed to HSCT (i.e. it is not appropriate to include an adjustment for HSCT effects in patients who have not undergone HSCT). Additionally, the analysis ignores known information from the propensity score indirect analysis on overall survival treatment effects in patients who undergo HSCT (HR 1.033; 95% CI 0.611, 1.748) or who do not proceed to HSCT (HR 0.405; 95% CI 0.165, 0.995).</p>	High, direction unclear
Health state costs	<p>The resubmission included revised disease management costs associated with relapse-free/relapsed disease and MRD status using new estimates for utilisation of healthcare visits (from a sponsor-commissioned Australian physician survey) but retained hospitalisation visits (based on UK physician interviews). It was unclear why patients in complete remission (MRD- or MRD+) would be hospitalised for reasons other than HSCT, treatment or the management of adverse events (which are already accounted for in other parts of model). In addition, the costs were estimated using inadequately justified assumptions (e.g. patients achieving an MRD response remained MRD negative until relapse or death, short-term monitoring intensity sustained in the long term). Overall, there were substantial differences in the costs for MRD+ versus MRD- patients in the relapsed free health state (\$39,000 versus \$7,000 per year for the first five years that a patient is in this state) that were not adequately justified.</p> <p>The resubmission included MRD response in the consolidation chemotherapy arm (8% MRD+) based on expert advice indicating that no more than 10% of patients achieve a delayed response with maintenance therapy. The expert advice was not provided with the resubmission and it was unclear whether the estimated response rate was based on consolidation and/or maintenance chemotherapy. On the other hand, 92% of patients in the blinatumomab arm were assumed to be MRD+ in the relapse free state.</p>	High, favours blinatumomab
Utility values	The estimated utilities were 0.806 for relapse free disease and 0.692 for relapsed disease (unchanged from July 2018 submission). The utility estimates were derived using a complex series of steps and transformations using propensity-matched populations that could not be validated. Unadjusted utility values for the BLAST study and TOWER trial were not provided in the resubmission.	High, favours blinatumomab

Source: Constructed during the evaluation

Abbreviations: B-ALL, B-cell lymphoblastic leukaemia; HSCT, haematopoietic stem cell transplant; MRD, minimal residual disease; Ph+, Philadelphia chromosome positive.

6.48 The key differences between the resubmission and the July 2018 submission and changes that were made to address the PBAC’s previous concerns are outlined in the table below.

Table 11: Key changes made in the economic model to address the PBAC’s previous concerns

Previous submission and PBAC consideration [Paragraph 6.60]	Resubmission
Survival outcomes based on ATT analysis. PBAC considered ATE would be more appropriate	ATE analysis used. This was appropriate.
The 3 phase estimation of survival. PBAC considered this may not be reliable given structural issues	Simplified extrapolation of survival curves using parametric functions. The ESC considered that the simplification of the extrapolation approach was reasonable. However, the implication of convergence between RFS and OS in the blinatumomab arm was not clinically plausible.
Lack of documentation or validation to support utilities	Additional documentation provided to support the derivation of the utility values
Cost issues	
PBAC considered the treatment, downstream management, salvage therapy and health state costs may not be reliable given substantial uncertainties with the sources and calculations of all costs.	Updated health state (non-drug) costs using healthcare resource utilisation estimates from a sponsor-commissioned Australian physician survey.
- Consolidation chemotherapy: based on ALLG ALL6 (assuming 100% dose intensity), which may not reflect clinical practice	Based on a modified hyper-CVAD (Cycles 3-8 only; assuming 80% dose intensity). The ESC considered this was appropriate given the hyper-CVAD regimen is current standard of care in the Australian adult population and noting not all patients would complete the full course in clinical practice.
- The economic model assumed that all relapse-free patients would receive maintenance therapy for 2 years based on the ALLG ALL6 protocol	Removed maintenance chemotherapy drug costs. The ESC noted that, while this approach was consistent with the efficacy data from the BLAST study, it was inconsistent with the proposed clinical algorithm where maintenance chemotherapy is proposed for both arms where a patient does not proceed to HSCT.
- Underestimated hospitalisation costs for blinatumomab administration (4 days for administration)	Increased to: 5 days for administration, 8.6 days for CSF prophylaxis, 2.3 days for AEs.
- Did not address the costs, accuracy and impacts of MRD testing.	Included MRD monitoring costs in blinatumomab arm (\$808).
- Blinatumomab pre-medication and intrathecal prophylaxis costs not included	Included
- AE costs should have been included	Same AE costs used in both arms

Source: Constructed during preparation of the ESC advice

6.49 Although the resubmission addressed each of the issues with the economic evaluation identified by the PBAC in its consideration of the previous submission (Blinatumomab PSD July 2018, para 6.60), the following issues were not adequately addressed and remain outstanding:

- The lack of evidence to support a statistically significant improvement in overall survival for blinatumomab in the ATE analysis. The PSCR argued that whilst the results of the ATE weighted analysis for overall survival did not reach statistical significance, a numerical improvement in favour of blinatumomab was observed with the upper confidence interval only marginally exceeding the point of significance. The ESC considered the appropriateness of including an overall

survival benefit was dependent on: whether the indirect comparison is considered reliable (e.g. whether the results may be confounded by historical control data which may not reflect outcomes in current Australian practice); and whether the plateau observed in the overall survival curve of the updated BLAST study data (see paragraph 6.31) could be reasonably assumed to represent longer-term, durable overall survival;

- Whether the modelled population and circumstances of use are representative of the target PBS population. For example, the ESC noted that the base case of the model was based on patients in first relapse only; a sensitivity analysis based on patients in second and third relapse only increased the ICER from \$75,000/QALY - \$105,000/QALY to \$105,000/QALY - \$200,000/QALY;
- The adjustment of relapse-free survival to not exceed overall survival in the blinatumomab arm only (discussed further below);
- The lack of a time on treatment curve;
- The inclusion of HSCT as a cost item rather than an event in the model (discussed further below);
- The reliability of health state costs given substantial uncertainties with the sources and calculation of costs (discussed further below); and
- Poor documentation and limited validation of a complex multi-step approach to estimating utility values (discussed further below).

6.50 In addition to concerns previously raised by PBAC there are number of other issues associated with the updated economic model:

- the potentially higher number of treatment days with blinatumomab in the ATE-weighted versus overall population;
- the inclusion of Ph+ drug costs in the comparator arm while the rest of the model was based on a Ph- population;
- uncertainty with the estimated costs, accuracy and likely impacts on health outcomes due to MRD testing;
- the use of equivalent adverse event costs assuming non-inferior safety between treatment arms; and
- costs of salvage therapy given the availability of blinatumomab and inotuzumab.

6.51 To address the PBAC's previous concerns about structural issues with the previous 3-phase approach, the resubmission used a simplified extrapolation of survival curves using parametric functions. The ESC noted that survival in the consolidation chemotherapy arm was estimated from Kaplan-Meier data for the ATE-weighted population of the historical control (0 to 4 years) with long term survival extrapolated using parametric survival functions (fitted to ATE-weighted survival data from 0-10 years from the historical control). The treatment effect of blinatumomab compared

to consolidation chemotherapy was based on the propensity score indirect analysis using ATE weights (0-4 years) and the assumption of no difference in hazards between treatments beyond 4 years. The ESC considered the revised extrapolation of survival was less uncertain than the previous submission that required major adjustments to reconcile values. However, the ESC considered that issues remained with the approach used, particularly the requirement to adjust relapse-free survival to not exceed overall survival in the blinatumomab arm (as outlined in Paragraphs 6.62 to 6.63).

- 6.52 The PBAC previously considered that HSCT should be included as an event in the model, rather than just a cost item (Blinatumomab PSD July 2018, para 6.60). The resubmission continued to exclude HSCT as an event in the model stating that it would increase uncertainty given the limited data to inform any assumptions and that it is not possible to discern the relative impact of blinatumomab and HSCT on the overall treatment effect observed. The resubmission stated that HSCT was included as a cost item only because the outcomes included in the model are derived from datasets where HSCTs occurred, therefore the risks and benefits are implicit to the model. The resubmission estimated the cost of HSCT based on the transplant rates from the studies (72.6% in BLAST versus 38.4% in historical control). While the ESC acknowledged there was likely insufficient data to model HSCT as an event reliably, the ESC considered that the impact (the direction and magnitude of effect on the ICER) of not including HSCT as an event was unknown and this introduced uncertainties into the model.
- 6.53 The PBAC previously considered that there was a lack of adequate documentation in the previous submission to support utility values estimated through a complex multi-step approach and noted that overall EQ-5D results for the BLAST study were not provided (Blinatumomab PSD July 2018, para 6.60). To address this issue, the resubmission provided additional documentation and validation of these estimates. The utility estimate for relapse-free disease was not adequately supported as it included inappropriate covariate analysis, had poor accounting of data loss, and the ATT analysis was used for utilities versus ATE for the rest of the economic model. The utility estimate for relapsed disease was not adequately supported as it was based on a complex multi-step approach with propensity score matching between BLAST and TOWER, poor accounting of data loss and resulted in an estimate substantially worse than previously estimated in the blinatumomab submission for relapsed/refractory disease (0.69 for 'relapsed disease' in the resubmission versus 0.84 in the July 2016 submission for relapsed/disease in the 'before relapse' health state). Unadjusted utility values for the BLAST study and TOWER trial were not provided in the resubmission.
- 6.54 The PSCR argued that a review of utility estimates from the published literature undertaken for the resubmission validated the trial-based utility estimates. The ESC noted that the PSCR provided further clarification around the method used to derive utility estimates, though there remained inadequate justification for using ATT data to derive utility estimates. Further, the ESC noted that the utility values were derived

from the UK-based preference weights for the EQ-5D, which are considered to be outliers to international scores due to the broad spread of utility weights relative to algorithms from other countries including Australia. The ESC noted that the ICER was sensitive to changes in utility values, and considered that the utilities applied were unlikely to have been conservative.

- 6.55 The resubmission provided revised estimates of disease management costs associated with relapse-free/relapsed disease and MRD status based on a sponsor-commissioned survey of Australian physicians and interviews with UK physicians. The estimated numbers of hospitalisations by MRD status from both sources do not appear plausible. It was unclear why patients in complete remission (MRD- or MRD+) would be hospitalised for reasons other than HSCT, treatment or the management of adverse events (which are already accounted for in other parts of model). Additionally the assumption that patients who are MRD+ have the same level of hospitalisations as patients with relapsed disease also appears implausible and is inconsistent with the Australian data showing higher health resource use for relapsed patients. The estimated number of specialist and GP visits by MRD and relapse status may be reasonable in the short term but it is unclear whether this intensity of monitoring would be maintained long term.
- 6.56 The PSCR claimed that patients with ALL are heavy users of inpatient services and the extent of hospitalisation applied to MRD positive patients in the model of approximately 1 admission every 3 months is relatively modest and consistent with a recent chart US chart review by Rose et al., 2018 (average of 1.9 days per patient per month). However, limited information were available regarding Rose et al, 2018 which was only provided as a poster presentation, and it was unclear whether the reported hospitalisations represent resource use associated with the underlying health state or resource use associated with treatment administration and adverse events (which are accounted for separately in the model).
- 6.57 Further, the ESC noted that the total disease management costs accrued were high in the consolidation chemotherapy arm, particularly in the relapsed health state (where costs accrued were \$54,299 higher in the consolidation chemotherapy arm (\$64,141) versus the blinatumomab arm (\$9,842), refer to Table 12). The ESC noted this was due to: the high cost per cycle in the relapsed health state (\$39,000 per year, applied for the entire duration that the patient remains in this health state); and that the model did not allow patients in the blinatumomab arm to be in the relapsed disease health state after 8 years, while patients in the consolidation chemotherapy arm could remain in the relapsed state for the entire time horizon of the model (the latter is discussed further in Paragraph 6.62 to 6.563. Overall, the ESC considered the disease management costs were overestimated, with that overestimate being considerably higher in the consolidation chemotherapy arm (hence yielding a significant cost offset that is unlikely to accurately reflect the true offset).
- 6.58 Table 12 summarises the incremental costs for health care resource items used in the economic evaluation.

Table 12: Health care resource items: disaggregated summary of cost impacts in the economic evaluation

Type of resource item	Blinatumomab	Consolidation chemotherapy	Incremental cost
Drug costs	\$ █████	\$ █████	\$ █████
Administration costs	\$9,895	\$21,657	-\$11,762
Intrathecal chemotherapy prophylaxis ^a	\$15,968	\$0	\$15,968
MRD test costs	\$808	\$0	\$808
Adverse event costs	\$4,551	\$4,551	\$0
Transplant costs	\$135,342	\$71,586	\$63,756
Salvage chemotherapy for recurrent disease	\$45,170	\$49,912	-\$4,742
Relapse-free management costs	\$36,928	\$58,047	-\$21,118
- MRD positive	\$21,205	\$57,103	-\$35,898
- MRD negative	\$15,723	\$944	\$14,779
Relapsed disease management costs	\$9,842	\$64,141	-\$54,299
Total costs	\$ █████	\$ █████	\$ █████

Source: Table 78, p177 of the resubmission

^a Intrathecal chemotherapy prophylaxis costs are included in drug costs and administration costs for consolidation chemotherapy

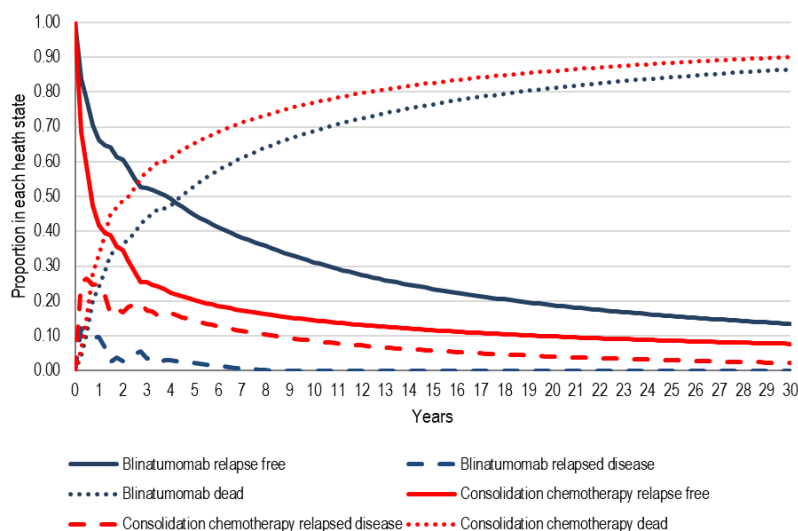
Note: The costs of intrathecal chemotherapy prophylaxis for blinatumomab were corrected during the evaluation for an error in the model (per cycle costs were applied to relapse free years, rather than the proportion of patients in the relapse-free health state)

Abbreviations: MRD, minimal residual disease

6.59 The difference in cost between treatment arms was largely driven by increased drug costs and transplant costs in the blinatumomab arm, which was partially offset by reductions in relapse-free and relapsed disease management costs.

6.60 A Markov trace of the proportion of patients in each health state over time is presented below.

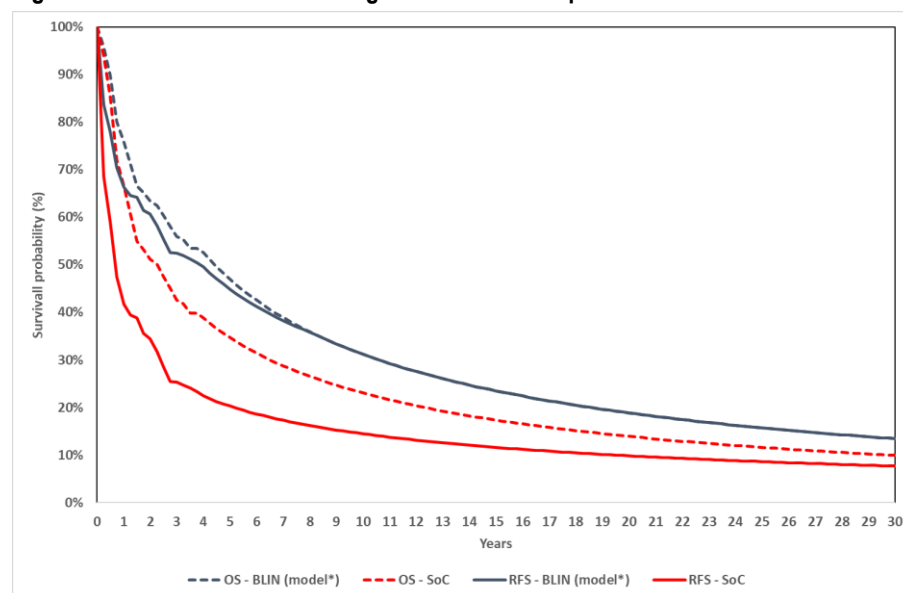
Figure 3: Markov trace of the proportion of patients in the relapse-free, relapsed disease and dead health states



Source: Figure 35, p175 of the resubmission

6.61 The modelled survival curves for relapse-free survival and overall survival are presented below

Figure 4: Survival curves informing the model for relapse free survival and overall survival



Source: Figure 30, p135 of the resubmission

- 6.62 The Markov trace (Figure 3) demonstrated a rapid separation of curves in the first four years with a slow trend towards convergence over the course of the model. The modelled survival curves (Figure 4) indicated that, in the blinatumomab arm, the relapse free survival curve was converged with the OS curve at 8 years. This was because the approach used to extrapolate survival resulted in higher relapse-free survival compared to OS (at approximately 8 years in the model) in the blinatumomab treatment arm. To address this, the model included an adjustment factor to prevent relapse-free survival exceeding OS (which essentially assumed that all patients on blinatumomab who relapse die immediately). This meant that patients in the blinatumomab arm could not be in the relapsed state after 8 years, while patients in the consolidation arm could remain in (or enter) the relapsed state for the entire time horizon of the model.
- 6.63 The ESC considered that the model trace in which OS and relapse free survival for blinatumomab are identical beyond 8 years was not clinically plausible as, in clinical practice, patients would have a period of time between relapse and death (albeit short in some cases). Further, the ESC considered that the lack of patients alive post-relapse in the blinatumomab arm, but not the consolidation chemotherapy arm, generates a significant cost offset from there being no further disease management costs (in the relapsed health state after 8 years) in the blinatumomab arm only. The ESC considered that this difference in disease trajectory between treatment arms was not adequately supported by available clinical data. The ESC reiterated its previous view that that the need for adjustments to the survival curves suggested that the underlying data did not adequately reflect the implicit relationships between survival estimates. (Table 12, blinatumomab July 2018 PSD).
- 6.64 Notwithstanding this, the ESC considered it was not clinically plausible for many patients (in either arm) to be in the relapsed health state after about 8 to 10 years as

most relapses occur in the first few years following initial treatment and relapsed disease is associated with high mortality. As such, the ESC considered that the proportion of patients in the relapsed disease health state in the consolidation chemotherapy arm beyond 8 to 10 years was overestimated. The ESC noted that the resubmission did not attempt to validate the model traces using data from other external sources on patient survival with B-ALL.

- 6.65 Table 13 summarises the results of the modelled economic evaluation presented in the July 2018 submission, and the results of the modelled economic evaluation in the resubmission.

Table 13: Results of the economic evaluation for the previous submission, current resubmission and alternative base case for blinatumomab versus consolidation chemotherapy

Type of resource item	Blinatumomab	Consolidation chemotherapy	Incremental difference
Previous submission: Results of the economic evaluation presented in the July 2018 submission			
Costs	██████████	██████████	██████████
Life years	6.7337	4.6791	2.0546
QALYs	5.3820	3.6086	1.7734
Incremental cost per QALY gained			██████████
Results of the economic evaluation presented in the current resubmission			
Costs	██████████	██████████	██████████
Life years	5.9900	4.7025	1.2875
QALYs	4.7995	3.6047	1.1948
Incremental cost per QALY gained			██████████

Source: Table 91, p163 of the July 2018 submission, Table 77, p177 of the resubmission

Abbreviations: QALYs, quality adjusted life years

The resubmission's base case was corrected for an error in the model in the calculation of intrathecal chemotherapy prophylaxis costs for blinatumomab (per cycle costs were applied to relapse free years, rather than the proportion of patients in the relapse-free health state)

- 6.66 Based on the economic model presented in the resubmission, treatment with blinatumomab was associated with a cost per QALY gained of \$75,000/QALY - \$105,000/QALY compared to consolidation therapy for the treatment of patients with B-ALL in haematological complete remission with minimal residual disease. This compares to a cost per QALY gained of \$45,000/QALY - \$75,000/QALY in the July 2018 submission.
- 6.67 The pre-PBAC response proposed a higher rebate on the published price of blinatumomab (increased from ██████% to ██████%), which reduced the ICER to \$75,000/QALY gained - \$105,000/QALY gained.
- 6.68 The results of key sensitivity analyses are summarised below. A multivariate sensitivity analysis, conducted during evaluation, is also presented assuming no overall survival benefit for blinatumomab (consistent with data from the propensity score indirect analysis), and removing the costs of imatinib from the consolidation chemotherapy arm (as this was the only component of the economic model that was specific for Ph+ patients).

Table 14: Results of key sensitivity analyses

	Incremental costs	Incremental QALYs	ICER
Base case		1.1948	
Univariate sensitivity analyses			
RFS efficacy (base case HR=0.47)			
- 95% upper CL (HR=0.73)		1.0281	
- 95% lower CL (HR=0.30)		1.2201	
Overall survival (base case HR=0.68)			
- no difference (HR=1)		0.1800	
- 95% upper CL (HR=1.09)		-0.0626	
- 95% lower CL (HR=0.42)		2.1493	
Overall survival extrapolation (base case curves do not converge at model endpoint of 30 years)			
- convergence starts at 4 years and ends at 30 years		1.2720	
- convergence starts at 4 years and ends at 20 years		1.0072	
- convergence starts at 4 years and ends at 10 years		0.6307	
Complete response (base case includes patients in first complete response only)			
- Patients in CR2/3 (higher baseline risk)		0.9488	
Time horizon (base case 30 years)			
- 5 years		0.4647	
- 10 years		0.7919	
- 20 years		1.0812	
Health state costs (base case: inpatient costs based on UK estimates; physician visits based on Australian survey; relapse free MRD+ costs higher than relapse free MRD- costs)			
- MRD+ inpatient costs based on MRD- inpatient costs		1.1948	
- all MRD+ costs based on MRD- costs		1.1948	
Relapse free utility (base case 0.806)			
- 0.70		0.9123	
- 0.75		1.0455	
- 0.85		1.3121	
Relapsed disease utility (base case 0.692)			
- 95% lower CL (0.649)		1.2540	
- 95% upper CL (0.734)		1.1369	
Multivariate sensitivity analysis			
No overall survival benefit for blinatumomab; imatinib costs removed		0.1800	

Source: Tables 83-84, p182-184 of the resubmission and calculations performed during the evaluation using BlinMRD_Section3model_October2018 spreadsheet

Abbreviations: blin., blinatumomab; CL, confidence limit; HR, hazard ratio; HSCT, haematopoietic stem cell transplant; MRD, minimal residual disease

Note: Results corrected for an error in the model in the calculation of intrathecal chemotherapy prophylaxis costs for blinatumomab (per cycle costs were applied to relapse free years, rather than the proportion of patients in the relapse-free health state)

6.69 The model was most sensitive to the treatment effect associated with blinatumomab on survival outcomes compared with consolidation chemotherapy. The model was also sensitive to time horizon, health state costs, hospitalisation costs, utilities and adjusting baseline risk for patients in second or subsequent complete response.

6.70 When the resubmission's model is revised to reflect no overall survival benefit for blinatumomab and to remove the costs of imatinib for Ph+ consolidation chemotherapy patients, the cost per QALY gained is more than \$200,000/QALY.

Drug cost/patient/course

- 6.71 The estimated drug cost for blinatumomab per patient per course was \$ [REDACTED] (based on 53 treatment days using the effective price of \$ [REDACTED] per vial per day; weighted between the private setting (41% at \$ [REDACTED]) and public hospital use (59% at \$ [REDACTED]). This is a small increase compared to the July 2018 submission (\$ [REDACTED] per patient per course; \$ [REDACTED] effective price per vial) due to updated PBS utilisation data (Oct 2018) for the private and public hospital settings.
- 6.72 The estimated drug cost for consolidation chemotherapy per patient per course for Ph- patients was \$10,728 (assuming 80% dose intensity; based on hyper-CVAD consolidation protocol using current DPMQ/DPMA: \$13,409). In the July 2018 submission, the estimated drug cost for consolidation chemotherapy per patient per course for Ph- patients was \$4,094 (based on ALLG ALL6 consolidation protocol, assuming 100% dose intensity).
- 6.73 The estimated drug cost for consolidation chemotherapy per patient per course for Ph+ patients was \$24,156 (assuming 80% dose intensity; based on hyper-CVAD consolidation protocol using current DPMQ/DPMA: \$13,409, plus imatinib 600 mg daily, using current DPMQ for 9.13 scripts of imatinib 400 mg packs: \$16,786). In the July 2018 submission, this was estimated to be \$26,783 (based on ALLG ALL6 consolidation protocol, assuming 100% dose intensity plus imatinib 600 mg daily, using current DPMQ for 9.13 scripts of imatinib 400 mg packs: \$22,690)

Estimated PBS usage & financial implications

- 6.74 This submission was not considered by DUSC. The resubmission used an epidemiological approach, using the same model and sources as the July 2018 submission to estimate the utilisation and financial implications of PBS listing blinatumomab for the treatment of patients with B-ALL in haematological complete remission with minimal residual disease. The estimated number of patients likely to be treated with blinatumomab was higher than estimated in the July 2018 submission due to higher assumed uptake of blinatumomab (increased from [REDACTED]% to [REDACTED]%), and larger proportions of paediatric patients assumed to achieve complete remission with MRD. The increase in uptake rate was in response to PBAC concerns that this was likely underestimated in the previous submission (Blinatumomab PSD July 2018, para 6.70). The ESC considered the revised uptake rate was more likely to reflect uptake in clinical practice.
- 6.75 The resubmission did not address some of the issues related to the estimated usage and financial implications identified by the PBAC at the July 2018 meeting (Blinatumomab PSD July 2018, para 6.70-6.71):
- The resubmission used the same simple extrapolation based on an assumed increase of 4-5 patients per year. Historical AIHW incidence data used to support the assumed annual increase excluded 2014 data (which became available during evaluation), and most likely underestimated the eligible population. The ESC noted that including the new data for 2014 (and using the same linear extrapolation used

in the resubmission), only slightly increased the estimated number of treated patients in Year 6 from less than 10,000 to less than 10,000 patients.

- The resubmission used the same four conditional multipliers for non-independent populations as the July 2018 submission (i.e. proportions of patient with B-cell lineage, immature B-cell precursor, in complete remission with MRD positivity, eligible for treatment), most likely underestimating the eligible population.
- The resubmission only included patients in first complete remission in the estimated use and financial implications to the PBS, most likely underestimating the eligible population.
- The resubmission assumed that each patient will receive 2 cycles (53 vials) of blinatumomab, based on exposure in the BLAST study, while patients are eligible for up to four cycles of blinatumomab (112 vials) under the requested restriction. The ESC considered that in clinical practice, patients would likely receive a larger number of vials of blinatumomab compared to patients in the BLAST study. The ESC noted that, in the BLAST study, a large proportion of patients went to transplant post cycle 1 or 2, whilst in Australian clinical practice most will undergo transplant after 2 to 4 cycles, and thus there will be more cycles per patient in the likely PBS population. The pre-PBAC Response stated that the proposed RSA would help address uncertainties regarding the average number of cycles of blinatumomab.

- 6.76 Table 15 summarises the estimated extent of use and costs of listing blinatumomab for the treatment of patients with B-ALL in haematological complete remission with minimal residual disease in the first 6 years of listing.
- 6.77 The ESC considered the estimated percentage of MRD positive adult and paediatric patients to be uncertain as there is wide variability in the reported proportion of patients with post induction MRD (30-50% adults and 10-20% paediatric patients).

Table 15: Estimated use and financial implications (based on price proposed in the resubmission)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated eligible patient population						
Incidence of ALL (All)	■	■	■	■	■	■
- Adults	■	■	■	■	■	■
- Paediatrics	■	■	■	■	■	■
Eligible patients (All)	■	■	■	■	■	■
- Adults (24.82%)	■	■	■	■	■	■
- Paediatrics (13.57%)	■	■	■	■	■	■
Estimated extent of use and cost of blinatumomab on the PBS						
Total number of patients (95% uptake)	■	■	■	■	■	■
Total number of vials (53 vials) ^a	■	■	■	■	■	■
Total expenditure (effective, \$/unit)^b	■	■	■	■	■	■
Patient co-payments (\$23.51) ^c	■	■	■	■	■	■
Total cost to PBS (effective; no copayment)	■	■	■	■	■	■
Substituted chemotherapy costs ^d	■	■	■	■	■	■
Avoided salvage therapy costs	■	■	■	■	■	■
Net financial impact to PBS (effective, no copayment)	■	■	■	■	■	■
Previous submission - July 2018						
Total number of patients	■	■	■	■	■	■
Total cost to PBS	■	■	■	■	■	■
Net financial impact to PBS (less offsets)	■	■	■	■	■	■

Source: Tables 86, p.189; 89, p.194; 92, p.197; 94, p.200; 95, p.201; 99, p.205 and 100, p.206 of the resubmission.

Abbreviations: ALL, acute lymphocytic leukaemia.

^a Adjusted for proportion of vials used for hospital inpatients (4.81%).

^b Weighted mean price per unit between public and private hospital listed prices (59% public, 41% private).

^c Weighted patient copayment derived from beneficiary distribution of blinatumomab relapsed/refractory listing up to June 2018.

^d Substituted chemotherapy costs corrected for error in costs concomitant medication. Medication costs over the PBS copayment threshold inappropriately included patient copayments in savings to PBS.

- 6.78 The estimated cost to the PBS (drug cost only) was less than \$10 million (based on the effective price proposed in the resubmission) in the sixth year of listing with a cumulative cost over six years of \$30 - \$60 million. This is an increase compared to the July 2018 estimates of less than \$10 million in Year six with a cumulative cost of \$30 - \$60 million over six years.
- 6.79 The estimated cost to the PBS (less drug cost offsets) was less than \$10 million (based on the effective price) in the sixth year of listing, and \$20 - \$30 million over six years. This is a decrease compared to the July 2018 estimates of less than \$10 million in Year six (\$30 - \$60 million over six years; based on the effective price).
- 6.80 The estimated net financial impact of listing blinatumomab on the PBS was substantially reduced due to a modest increase in the cost offsets associated with substituted chemotherapies and a substantial increase in the cost offsets associated with the avoidance of salvage therapy for relapsed disease (i.e. use of blinatumomab

as salvage therapy for relapsed disease in patients who are not treated with blinatumomab in the MRD setting).

6.81 The evaluation considered that the financial impact was uncertain, and most likely underestimated, for the following reasons:

- The estimated eligible population was slightly larger than that estimated in the July 2018 submission, but remained underestimated. The estimates used the same four conditional multipliers for non-independent populations and used a low estimated proportion of post-induction MRD positivity reported in the four cited studies (40%) to estimate the proportions of adult patients likely to be MRD positive post-induction in the eligible Australian population.
- The number of vials per patient may have been underestimated as it was based on the BLAST study in which few patients completed four cycles of blinatumomab due to higher rates of HSCT, and earlier use of HSCT, than would occur in Australian clinical practice.
- The drug cost offsets derived from blinatumomab substitution of other chemotherapy regimens were overestimated, as the assumed 80% persistence in substituted chemotherapy regimens was based on relapse rates observed for older chemotherapy regimens in the historic cohort, which are likely to underestimate relapse rates in the Australian setting. In addition, patient copayments were inappropriately included in PBS cost offsets.
- The assumption of equivalent costs of managing adverse events associated with blinatumomab and standard of care chemotherapy was not reasonable as the clinical claim of non-inferior safety was not supported.
- The cost offsets derived from differential costs of salvage therapies for relapsed disease were poorly documented and likely overestimated. Cost estimates were derived from the economic model outputs and therefore incorporate uncertainties associated with the model. Additionally, the costs estimates include the impact of discounting which is inappropriate for budget impact estimates. Furthermore, the cost estimates for salvage therapy were applied to **all** patients in the **same** year as treatment for MRD that was inconsistent with both clinical data and the economic analysis. The assumption that standard of care patients will receive blinatumomab and blinatumomab patients will receive FLAG-ida salvage therapy may not be reasonable given that inotuzumab (recommended by the PBAC in November 2018) may be a treatment option as salvage chemotherapy for both treatment arms. Further, the PSCR noted that the estimated cost offsets for salvage therapy are only relevant if the restriction for blinatumomab includes a once per lifetime clause.
- The cost of hospitalisation for blinatumomab administration were underestimated. Blinatumomab hospitalisation was assumed to be at the minimum durations and instances recommended in the blinatumomab product information.

- 6.82 The sensitivity analyses presented in the resubmission showed that the estimated financial impact of listing blinatumomab on the PBS was most sensitive to changes in the number of vials of blinatumomab required for each treatment, consistent with the high unit cost of blinatumomab per vial (estimated cost of less than \$10 million in Year six; effective price). The estimated financial impact of listing blinatumomab was also sensitive to the assumption of once-in-a-lifetime use.

Quality Use of Medicines

- 6.83 The resubmission argued that limiting PBS subsidised blinatumomab to one course per lifetime between both the MRD and relapsed/refractory listings may result in patients who have responded well to blinatumomab in the MRD setting, being unable to receive blinatumomab in the relapsed/refractory setting. In addition, a once-in-a-lifetime rule may lead treating clinicians to reserve blinatumomab treatment for the relapsed/refractory setting. This is discussed in 'Requested listing'.

Financial Management – Risk Sharing Arrangements

- 6.84 The resubmission acknowledged the need for an amended Risk Share Arrangement to account for reduced blinatumomab use in the existing relapsed/refractory listing because of listing blinatumomab in the MRD setting.
- 6.85 The resubmission requested the PBAC consider listing blinatumomab for more than a once-in-a-lifetime treatment, and acknowledged that a revised Risk Sharing Arrangement may be appropriate for this kind of listing. The submission provided no further details. The PSCR stated that “the uncertainty associated with re-treatment can be managed by an appropriate cap on expenditure which would limit the extent to which the PBS is subject to this uncertainty whilst also providing the opportunity for physician and patients to use this treatment option if clinically appropriate”.
- 6.86 The pre-PBAC Response stated that the sponsor “is willing to agree financial caps for blinatumomab with the expanded listing that reflect new use in the MRD setting and, as requested by the PBAC, a decline in use in the R/R setting.” The pre-PBAC response further stated that the “ALL treatment pathway is complex and it is difficult to determine what the impact of the MRD listing will be on use of blinatumomab in the R/R setting. In addition, the practice change of using blinatumomab in MRD, and associated decline in use of blinatumomab in R/R, will take several years to reach steady state. For these reasons, Amgen’s preference is for a single deed and one set of caps for blinatumomab.”
- 6.87 The sponsor’s proposed overall caps for blinatumomab are shown in Table 16. The pre-PBAC Response stated that these caps reflect the sum of the MRD setting base case financial estimates and established caps in the relapsed/refractory setting with the latter reduced by █%. The pre-PBAC Response proposed █% rebates above the overall cap.

Table 16: Proposed overall caps for blinatumomab (from the pre-PBAC response)

	Year of expanded listing ¹				
	1	2	3	4	5
MRD submission base case estimates [A] ²	██████████	██████████	██████████	██████████	██████████
R/R caps ³ [B]	██████████	██████████	██████████	██████████	██████████
[A] + [B]	██████████	██████████	██████████	██████████	██████████
Proposed overall caps adjusted for changing treatment patterns	██████████	██████████	██████████	██████████	██████████

Source: Table 1 p2 of the pre-PBAC Response

Abbreviations: MRD, minimal residual disease; R/R, relapsed or refractory

¹Year 1 of the expanded listing corresponds to Year 1 for listing in the MRD setting and Year 3 for listing in the R/R setting

² Current submission base case estimates adjusted for proposed 24% rebate within the financial analysis workbook.

³ Corresponds to current R/R caps in deed with calculation of impact of rebate increase, i.e. caps x (1-██████████)/(1-██████████). Caps are forecasted a further 2 years based on percentage increase in prior years.

For more detail on PBAC’s view, see section 7 PBAC outcome.

7 PBAC Outcome

- 7.1 The PBAC deferred making a recommendation on the Section 100 Authority Required (Efficient Funding of Chemotherapy) listing of blinatumomab for the treatment of patients with B-cell precursor acute lymphoblastic leukaemia (B-ALL) in haematological complete remission with minimal residual disease (MRD) following induction chemotherapy. This was to request further information from the sponsor on issues around the estimated incremental cost-effectiveness ratio (ICER), overall net financial implications and proposed Risk Share Arrangement (RSA). The PBAC considered that the ICER was high, uncertain and likely underestimated. The PBAC considered that blinatumomab would only be cost-effective if the price was reduced, and financial arrangements were put in place to ensure that savings due to reduced use of blinatumomab in the relapsed/refractory (R/R) setting would be realised. In deciding to defer, the PBAC acknowledged that no further comparative data were likely to be forthcoming and there was unlikely to be sufficient information to construct an economic model that would reliably model the condition.
- 7.2 The PBAC noted the high risk of relapse in patients with MRD positive disease, and that use of blinatumomab in the MRD setting would prevent or delay a proportion of use in the R/R setting. The PBAC also considered that an important role for blinatumomab was as a bridge to transplant, and considered that use of blinatumomab in the MRD setting may result in more patients receiving a HSCT in a better risk state.
- 7.3 Overall, the PBAC reiterated that there is a high clinical need for more effective treatments for B-ALL in the first-line setting where there is the greatest potential for impact on cure rates.
- 7.4 The PBAC noted there is clinical evidence (Topp et al., 2018) indicating that blinatumomab retreatment may be effective for patients with prior response to blinatumomab in the R/R setting. As such, the PBAC considered it would be clinically appropriate to allow retreatment in the R/R setting for patients who responded to

blinatumomab in the MRD positive setting. The PBAC further considered that an adequate response to blinatumomab in the MRD setting would constitute a relapse free period of at least 6 months following completion of blinatumomab treatment, and recommended that this be specified in the restriction.

- 7.5 The PBAC maintained that the appropriate eligible population should include both Ph+ and Ph- patients. The PBAC noted that TKIs are part of standard of care treatment for patients with Ph+ B-ALL, and clinical evidence in the R/R setting indicates that concomitant use of blinatumomab with a TKI is associated with a tolerable safety profile. As such, the PBAC agreed with the ESC that the restriction should allow concomitant use of blinatumomab and a TKI.
- 7.6 The PBAC noted that the comparative effectiveness continued to be based on a propensity score indirect analysis comparing blinatumomab (based on the BLAST study) with standard of care chemotherapy (based on Study 20120148, a historical control). The PBAC noted that the resubmission had used the average treatment effect (ATE) method as the primary analysis, consistent with the PBAC's advice in July 2018. However, the PBAC considered that the resubmission had not addressed many of its previous concerns with this analysis including potential: issues with the applicability of the standard care chemotherapy arm to Australian clinical practice; differences between the population included in the propensity score analysis and the PBS population; and a high risk of bias.
- 7.7 The PBAC recalled its previous consideration that the magnitude of any improvement in overall survival could not be reliably determined from the propensity score analysis given: it was informed by immature data from the BLAST study (median follow-up of 18.3 months); it was confounded by HSCT use; and there were issues limiting the reliability of the indirect comparison (as outlined in the previous paragraph). Further, the PBAC noted that the overall survival gain in the ATE analysis was not statistically significant (HR 0.68; 95% CI 0.42, 1.09).
- 7.8 Notwithstanding these limitations, the PBAC considered that the ATE analysis was likely to be the most reliable comparative data available, noting the resubmission's advice that randomised control data in this treatment setting would no longer be forthcoming as the ongoing studies of blinatumomab in this setting were amended from randomised controlled phase III trials to single arm studies.
- 7.9 The PBAC noted that the PSCR provided updated survival data from the single-arm BLAST study that showed a median overall survival of 36.5 months (95% CI 22.0, not estimable) with a median follow up of 4.5 years. These data showed that overall survival was similar regardless of whether or not patients received HSCT (in patients in continuous complete remission, Figure 3). However, the PBAC noted that the causes of death differed: mortality in patients who did not undergo HSCT was largely due to relapse; while mortality in patients who underwent HSCT was mainly in relapse-free patients and likely due to HSCT complications (Figure 4). The PBAC noted that the majority of patients who underwent HSCT in continuous complete remission were relapse-free at the time of the data-cut and considered it was plausible that some of

these patients may have a durable long-term survival. Thus, the PBAC considered that these updated data provided a clearer indication that blinatumomab may be associated with an overall survival advantage. However, the PBAC considered that it remained unclear whether blinatumomab would lead to long-term gains in overall survival given the lack of reliable comparative data and the relative immaturity of data from the BLAST study.

- 7.10 The PBAC reiterated its previous consideration that blinatumomab is effective at eliminating MRD and is associated with durable relapse-free survival.
- 7.11 The PBAC noted that the resubmission did not present any new clinical safety data. As such, the PBAC maintained its previous consideration that blinatumomab and standard of care chemotherapy have different safety profiles, where both are associated with potentially life-threatening complications.
- 7.12 The PBAC noted that the economic model included three health states: relapse-free disease, relapsed disease and death. HSCT was not included as a health state despite it being a treatment effect modifier, and a major clinical event with its own risks, benefits and costs. As outlined in Paragraph 7.9, the cause of death appeared to differ depending on whether a patient underwent HSCT. As such, the PBAC considered that the model did not adequately reflect the different treatment pathways that patients treated with blinatumomab would undergo depending on whether they underwent HSCT, relapsed, experienced HSCT complications, died or experienced long-term survival (as outlined in Paragraph 6.27). The PBAC considered that patients following different pathways would accrue different costs, and have different treatment outcomes (both risks and benefits), and that, in patients who undergo HSCT, some of these benefits may also be attributable to HSCT. While inclusion of data from the BLAST study may have implicitly included some of these effects, the PBAC considered that the costs, risks and benefits of the different treatment pathways would need to be modelled explicitly in order to accurately reflect the course of the disease and to reliably estimate cost-effectiveness. However, the PBAC acknowledged that there was unlikely to be sufficient data to reliably inform each of the treatment pathways.
- 7.13 The PBAC noted and agreed with the other issues raised by the evaluation and the ESC regarding the economic evaluation, as outlined in the 'Economic analysis' section, including:
- the model relied on an overall survival benefit that was uncertain;
 - there were applicability issues with the clinical data (e.g. the model was based on patients in first-relapse only which sensitivity analyses suggested underestimated the ICER/QALY);
 - the disease management costs were likely to have been significantly overestimated in the consolidation chemotherapy arm (which likely underestimated the ICER/QALY);

- there were structural uncertainties given the requirement to adjust relapse free survival to not exceed overall survival in the blinatumomab arm; and
 - the utility estimates were not adequately justified and unlikely to have been conservative.
- 7.14 Overall, the PBAC considered that the ICER/QALY was highly uncertain and likely underestimated.
- 7.15 The PBAC noted that the base case ICER was \$75,000/QALY - \$105,000/QALY gained and decreased to \$75,000/QALY - \$105,000/QALY gained with the additional rebate proposed in the pre-PBAC response. The PBAC recalled that blinatumomab was previously recommended in the R/R setting at an ICER of around \$45,000/QALY - \$75,000/QALY, which was based on a model informed by comparative data from a randomised controlled trial (TOWER). Noting the significant uncertainties with the clinical data and economic model that likely overestimated the ICER, the PBAC advised that the ICER in the MRD setting should not exceed that accepted in the R/R setting. Thus, the PBAC considered that a price reduction that results in an ICER less than \$45,000/QALY - \$75,000/QALY would be required.
- 7.16 Even with a lower ICER, the PBAC considered that the magnitude and durability of the overall survival benefit included in the model was highly uncertain, and it was unclear whether blinatumomab when used earlier in the treatment pathway would reduce long-term relapse rates and also therefore the use of subsequent therapies in the R/R setting. Thus, the PBAC considered that it could only be satisfied that blinatumomab was sufficiently cost-effective if financial arrangements were put in place to ensure that savings due to reduced use of blinatumomab in the R/R setting would be realised.
- 7.17 The PBAC noted that the estimated net cost to the PBS over six years was \$30 - \$60 million, which reduced to \$20 - \$30 million when PBS cost-offsets were included (for substituted consolidation chemotherapy and for avoided salvage therapy). The PBAC noted that the estimated cost-offsets were derived from the economic model outputs and therefore incorporated uncertainties associated with the model. The PBAC noted that the pre-PBAC response estimated that, if blinatumomab was listed in the MRD setting, there would be a ■■■% reduction in blinatumomab use in the R/R setting. The reduction in use appeared to be based on reduced use of blinatumomab: in patients who achieve MRD- status with blinatumomab and remain relapse-free; and in patients who do not achieve MRD- status and are therefore ineligible for blinatumomab in the R/R setting. The estimated ■■■% reduction also appeared to factor in re-treatment with blinatumomab in eligible patients who relapse. The PBAC considered that the pre-PBAC response had not provided sufficient information to determine how the ■■■% reduction was calculated, and requested that the sponsor provide further information to justify these estimates.
- 7.18 The PBAC noted that the pre-PBAC response had proposed a ■■■% rebate on expenditure above the subsidy caps and considered a ■■■% rebate was appropriate given the uncertain effect on blinatumomab use in the R/R setting, the uncertain

patient population and the likely underestimated number of vials per patient.

- 7.19 The PBAC noted that the evaluation had raised issues regarding the estimation of the size of the eligible population, but considered this was likely conservative in the context of these estimates being used to implement an RSA with a [REDACTED] % rebate above the subsidy caps. The PBAC considered that if a single RSA subsidy cap was to be enacted any increase in subsidy caps over that of the current R/R setting would need to account for both the increase in eligible patients due to MRD and the expected decrease in patients in the R/R setting.
- 7.20 In deferring making its decision on whether to recommend blinatumomab in the MRD setting, the PBAC considered the following issues would need to be addressed:
- a price reduction would be required to account for the uncertainties in the clinical data and economic model; and
 - further work was required to determine the appropriate reduction in the RSA caps in the R/R setting.
- 7.21 The PBAC advised that if the uncertainties with the clinical data and economic model could not be addressed through an appropriate price reduction and RSA arrangement, then a revised economic model would be required. The model would need to include HSCT as a health state and explicitly incorporate the different patient pathways outlined in Paragraph 7.12, and include the updated BLAST study data.

Outcome:

Deferred

8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

9 Sponsor's Comment

Amgen is pleased that the PBAC acknowledged the clinical need for effective treatment for B-ALL. The elimination of MRD with blinatumomab is an important and effective treatment option for these patients. As such, Amgen will continue to work with the PBAC with the aim to make blinatumomab available for these patients.