An addendum from the November 2024 PBAC meeting has been included at the end of this document.

6.01 BLINATUMOMAB, Powder for I.V. infusion 38.5 micrograms, Blincyto®, Amgen Australia Pty Limited.

1 Purpose of submission

1.1 The Category 2 submission requested an extension to the Section 100 (Efficient Funding of Chemotherapy) listing of blinatumomab for the treatment of patients with B-cell precursor acute lymphoblastic leukaemia (B-ALL) who are measurable residual disease (MRD) positive following induction chemotherapy, to include patients who are MRD-negative following induction chemotherapy.

1.2 Listing was requested on the basis of a cost-utility analysis of blinatumomab in combination with standard of care consolidation chemotherapy compared to standard of care consolidation chemotherapy alone.

Table 1: Key components of the clinical issue addressed by the submission (as stated in the submission)

Component	Description
Population	Newly diagnosed patients with B-ALL in haematological complete remission who are MRD-negative after initial induction chemotherapy
Intervention	Blinatumomab plus standard of care consolidation therapy
Comparator	Standard of care consolidation therapy (chemotherapy with or without ASCT)
Outcomes	Relapse-free survival, overall survival, and safety
Clinical claim	Blinatumomab added to standard of care consolidation therapy is superior in terms of efficacy and non-inferior in terms of safety compared to standard of care consolidation therapy alone

Source: Table 1-1, p21 of the submission.
Abbreviations: ASCT, allogeneic stem cell transplant; B-ALL, B-cell precursor acute lymphoblastic leukaemia; MRD, measurable residual disease.

2 Background

Registration status

2.1 **TGA status at time of PBAC consideration**: Blinatumomab for the treatment of newly diagnosed patients with B-ALL in MRD-negative haematological complete remission was submitted under the TGA/PBAC parallel process. The TGA Delegate's Overview is expected on 5 November 2024. At the time of evaluation, no TGA documents were available.

2.2 The requested indication is for the treatment of B-cell precursor acute lymphoblastic leukaemia (ALL) in the consolidation phase.

2.3 Blinatumomab is currently TGA-approved for the following indications:

- Relapsed or refractory B-cell precursor acute lymphoblastic leukaemia (ALL).

- Minimal residual disease (MRD)-positive B-cell precursor acute lymphoblastic leukaemia in patients in complete haematological remission.

2.4 The blinatumomab product information includes a black box warning for severe potentially fatal adverse events including cytokine release syndrome, neurological toxicities, and reactivation of JC polyomavirus. It is recommended that patients treated with blinatumomab should be closely monitored for signs and symptoms of associated adverse events (disseminated intravascular coagulation, capillary leak syndrome, haemophagocytic lymphohistiocytosis/macrophage activation syndrome and neurologic events) and treatment interrupted or ceased if severe or life-threatening toxic reactions are observed.

Previous PBAC consideration

2.5 Blinatumomab is listed on the PBS for:

- Relapsed/refractory B-ALL (listed in May 2017; amended in October 2019 to include the treatment of Philadelphia chromosome positive patients, after treatment with a tyrosine kinase inhibitor).
- MRD-positive disease in patients achieving complete remission following intensive combination chemotherapy for initial treatment of B-ALL or subsequent salvage therapy (listed in December 2019).

2.6 Following the recent public funding of MRD testing and changes in MRD testing technology, the blinatumomab MRD-positive PBS listing was updated to (i) align with the lowered threshold for detection of MRD (from 10^{-4} to 10^{-6}, if next generation sequencing is used), (ii) include a wider range of MRD testing methodologies by replacing the term 'polymerase chain reaction' with 'molecular methods', and (iii) replace the previously accepted term 'minimal residual disease' with the currently accepted 'measurable residual disease'. The terms 'measurable residual disease' and 'minimal residual disease' are used interchangeably in this document.

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

3 Requested listing

3.1 The requested restriction is based on the current blinatumomab MRD-positive B-ALL PBS listing, with amendments to eligibility criteria to allow for use regardless of MRD status. Changes to the current MRD-positive B-ALL PBS listing proposed by the sponsor are indicated by highlighted strikethrough for deleted text and highlight alone for added text. Suggested additions by the Secretariat are in italics and deletions are in strikethrough without highlight. The only exception to the latter is for the PBS indication in the flow on restriction changes where the sponsor suggested the PBS indication be Relapsed or refractory ALL and this highlighted suggestion has been deleted by the Secretariat.

MEDICINAL PRODUCT medicinal product pack	PBS item code	Dispensed Price Max Amt	Max. amount	№.of Rpts
Blinatumomab 38.5 microgram injection [1 vial] & inert substance solution [10 mL vial], 1 pack	Amend: 11850Q (Public) Amend: 11867N (Private)	Published price AEMP: $2,759.53 Public hospital: $77,355.46 Private hospital: $78,480.39 Effective price AEMP: $[redacted] Public hospital: $[redacted] Private hospital: $[redacted]	784 mcg	**1**
Available brands				
Blincyto (blinatumomab 38.5 µg injection, 1 vial)				

Category/Program:	Section 100 EFC: Public Hospital Private Hospital/Private Clinic
Prescriber type:	☒Medical Practitioners
Condition:	Acute lymphoblastic leukaemia (ALL)
PBS Indication:	~~Measurable residual disease of~~ Precursor B-cell acute lymphoblastic leukaemia (Pre-B-cell ALL) *in complete haematological remission (CR)*
Restriction Level/Method:	☒Authority Required - In Writing
Treatment phase:	Initial treatment ~~of measurable residual disease~~ of Pre-B-cell ALL
Treatment criteria:	Must be treated by a physician experienced in the treatment of haematological malignancies.
Clinical criteria:	Patient must have an ECOG performance status of 0 or 1,
	AND
Clinical criteria:	The condition must not be present in the central nervous system or testis,
	AND
Clinical criteria:	Patient must have achieved complete remission following intensive combination chemotherapy for initial treatment of acute lymphoblastic leukaemia (ALL) ~~or for subsequent salvage therapy,~~
	~~**AND**~~ ***OR***
Clinical criteria:	Patient must have *achieved complete remission following intensive combination chemotherapy and* have measurable residual disease based on measurement in bone marrow, documented after an interval of at least 2 weeks from the last course of systemic chemotherapy given as intensive combination chemotherapy treatment of ALL/as subsequent salvage therapy, whichever was the later, measured using flow cytometry/molecular methods,
	AND
Clinical criteria:	The treatment must not be more than 2 treatment cycles under this restriction in a lifetime.
Prescribing instructions:	According to the TGA-approved Product Information, hospitalisation is recommended at minimum for the first 3 days of the first cycle and the first 2 days of the second cycle.
Prescribing instructions:	For all subsequent cycle starts and re-initiation (e.g. if treatment is interrupted for four or more hours), supervision by a health care professional or hospitalisation is recommended.
Prescribing instructions:	An amount of 784 mcg will be sufficient for a continuous infusion of blinatumomab over 28 days in each cycle.
Prescribing instructions:	Blinatumomab is not PBS-subsidised if it is administered to an in-patient in a public hospital setting.
Prescribing instructions:	The authority application must be made in writing and must include: (1) a completed authority prescription form; and

	(2) a completed ~~Measurable residual disease positive~~ Acute Lymphoblastic Leukaemia *in complete haematological remission* PBS Authority Application - Supporting Information Form; and (3) date of most recent chemotherapy, and if this was the initial chemotherapy regimen or salvage therapy; and (4) the percentage blasts in bone marrow count that is no more than 4 weeks old at the time of application.
Prescribing instructions:	Patients who fail to demonstrate a response to PBS-subsidised treatment with this agent at the time where an assessment is required must cease PBS-subsidised therapy with this agent.
Notes:	A complete remission is defined as bone marrow blasts of less than or equal to 5%, no evidence of disease and a full recovery of peripheral blood counts with platelets of greater than 100,000 per microliter, and absolute neutrophil count (ANC) of greater than 1,000 per microliter.
Administrative advice:	No increase in the maximum number of repeats may be authorised.
Administrative advice:	No increase in the maximum quantity or number of units may be authorised.
Administrative advice:	Special Pricing Arrangements apply.
Administrative advice:	*Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).* *Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au* *Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos* *Or mailed to:* *Services Australia* *Complex Drugs* *Reply Paid 9826* *HOBART TAS 7001*
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.*
Category/Program:	Section 100 EFC: Public Hospital Private Hospital/Private Clinic
Prescriber type:	☒Medical Practitioners
Condition:	Acute lymphoblastic leukaemia (ALL)
PBS Indication:	~~Measurable residual disease of~~ precursor B-cell acute lymphoblastic leukaemia (Pre-B-cell ALL) *in complete haematological remission (CR)*
Restriction Level/Method:	☒Authority Required - Telephone ☒Authority Required - Electronic
Treatment phase:	Continuing treatment of previously ~~measurable residual disease of~~ Pre-B-cell ALL *in CR*
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
Clinical criteria:	Patient must have achieved a complete remission,

	AND
Clinical criteria:	The condition must be negative for measurable residual disease using the same method used to ~~determine initial PBS eligibility~~ *establish initial MRD status,*
	AND
Clinical criteria:	Patient must not have developed disease progression while receiving treatment with this drug for this condition,
	AND
Clinical criteria:	The treatment must not be more than 2 treatment cycles under this restriction in a lifetime.
Prescribing instructions:	For all subsequent cycle starts and re-initiation (e.g. if treatment is interrupted for four or more hours), supervision by a health care professional or hospitalisation is recommended.
Prescribing instructions:	An amount of 784 microgram will be sufficient for a continuous infusion of blinatumomab over 28 days in each cycle.
Prescribing instructions:	Blinatumomab is not PBS-subsidised if it is administered to an in-patient in a public hospital setting.
Prescribing instructions:	Patients who fail to demonstrate a response to PBS-subsidised treatment with this agent at the time where an assessment is required must cease PBS-subsidised therapy with this agent.
~~**Notes**~~ ***Administrative advice:***	Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).
Administrative advice:	No increase in the maximum number of repeats may be authorised.
Administrative advice:	No increase in the maximum quantity or number of units may be authorised.
Administrative advice:	Special Pricing Arrangements apply.
Notes:	*A complete remission is defined as bone marrow blasts of less than or equal to 5%, no evidence of disease and a full recovery of peripheral blood counts with platelets of greater than 100,000 per microliter, and absolute neutrophil count (ANC) of greater than 1,000 per microliter.*
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.*

Flow on changes to other blinatumomab PBS listings (11116C and 11118E):

Category/Program:	Section 100 EFC: Public Hospital Private Hospital/Private Clinic
Prescriber type:	☒Medical Practitioners
Condition:	Acute lymphoblastic leukaemia (ALL)
PBS Indication:	~~*Relapsed or refractory ALL*~~ *Acute lymphoblastic leukaemia*
Restriction Level/Method:	☒Authority Required - In Writing
Treatment phase:	Induction treatment
Treatment criteria:	Must be treated by a physician experienced in the treatment of haematological malignancies.
Clinical criteria:	The condition must be relapsed or refractory B-precursor cell ALL, with an Eastern Cooperative Oncology Group (ECOG) performance status of 2 or less,
	AND
Clinical criteria:	The condition must not be present in the central nervous system or testis,
	AND

Clinical criteria:	Patient must have previously received a tyrosine kinase inhibitor (TKI) if the condition is Philadelphia chromosome positive,
	AND
Clinical criteria:	Patient must have received intensive combination chemotherapy for initial treatment of ALL or for subsequent salvage therapy,
	AND
Clinical criteria:	Patient must not have received more than 1 line of salvage therapy,
	AND
Clinical criteria:	The condition must be one of the following: (i) untreated with this drug for ~~measurable residual disease~~ *Pre-B-cell ALL in CR*, (ii) treated with this drug for ~~measurable residual disease~~ *Pre-B-cell ALL in CR*, but the condition has not relapsed within 6 months of completing that course of treatment,
	AND
Clinical criteria:	The condition must have more than 5% blasts in bone marrow,
	AND
Clinical criteria:	The treatment must not be more than 2 treatment cycles under this restriction in a lifetime.
Prescribing instructions:	According to the TGA-approved Product Information, hospitalisation is recommended at minimum for the first 9 days of the first cycle and the first 2 days of the second cycle. For all subsequent cycle starts and re-initiation (e.g. if treatment is interrupted for 4 or more hours), supervision by a health care professional or hospitalisation is recommended.
Prescribing instructions:	An amount of 651 microgram will be sufficient for a continuous infusion of blinatumomab over 28 days in cycle 1. An amount of 784 microgram, which may be obtained under Induction treatment - balance of supply restriction, will be sufficient for a continuous infusion of blinatumomab over 28 days in cycle 2.
Prescribing instructions:	Blinatumomab is not PBS-subsidised if it is administered to an in-patient in a public hospital setting.
Prescribing instructions:	The authority application must be made in writing and must include: (1) a completed authority prescription form; and (2) a completed Acute Lymphoblastic Leukaemia PBS Authority Application - Supporting Information Form; and (3) date of most recent chemotherapy, and if this was the initial chemotherapy regimen or salvage therapy, including what line of salvage; and (4) if applicable, the date of completion of blinatumomab treatment for ~~measurable residual disease~~ *Pre-B-cell ALL in CR* and the date of the patient's subsequent relapse; and (5) the percentage blasts in bone marrow count that is no more than 4 weeks old at the time of application.
Notes:	Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos Or mailed to:

	Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7001
Administrative advice:	No increase in the maximum number of repeats may be authorised.
Administrative advice:	No increase in the maximum quantity or number of units may be authorised.
Administrative advice:	Special Pricing Arrangements apply.

3.2 The submission stated that the proposed effective AEMP per vial ($[redacted]) was based on the current pricing of blinatumomab in the relapsed/refractory setting. However, the proposed price is higher than the effective AEMP per vial in the relapsed/refractory setting ($), and the MRD-positive setting ($). The proposed listing allows use in both MRD-positive and MRD-negative settings; however, a weighted price was not proposed in the submission. The ESC considered the higher price proposed in the MRD-negative setting compared to the MRD-positive setting was not well justified. The ESC noted that thresholds and methods for MRD detection have changed since blinatumomab was recommended in the MRD-positive setting (i.e. recently established MBS items allow for MRD detection at lower thresholds for than those that were used in the key evidence supporting listing in this population). As such, there is likely to be a degree of overlap between the two settings, with the two populations not necessarily being distinct, and thus different prices may be difficult to justify. The pre-PBAC response offered a blinatumomab ex-manufacturer price of $ per vial in the MRD-negative setting.

3.3 Clinical criteria in terms of ECOG performance status, presence of disease in the CNS or testes, complete haematological remission following intensive combination chemotherapy, limit of 2 treatment cycles per lifetime (for each of the initial and continuing restrictions), and a response-based stopping rule (in the continuing restriction), are unchanged from the MRD-positive listing. Response to therapy is not defined. The ESC advised that if a separate restriction for MRD-negative patients is proposed then the continuing treatment restriction would not need a clinical criterion stating 'the condition must be negative for measurable residual disease using the same method used to establish initial MRD status'. However, the ESC considered a listing that covered both MRD-positive and MRD-negative patients was preferred. The pre-PBAC response considered a MRD-agnostic PBS listing appropriate.

3.4 The requested restriction is narrower than the proposed TGA indication, as it restricts access to patients with ECOG performance status of 0 or 1, achieving complete haematological remission, with no evidence of MRD in the CNS or testes. In addition, the requested restriction is not consistent with the population recruited in the key clinical trial (E1910), which included patients aged 30-70 years, with ECOG performance status of 0-2, and excluded patients who were Philadelphia chromosome (Ph) positive.

3.5 The submission acknowledged that no evidence was presented supporting the use of blinatumomab in MRD-negative patients aged less than 30 years, but argued that the unmet clinical need and limited treatment options outside of clinical trials for younger patients was appropriately addressed with an age-agnostic PBS listing. No evidence was presented for patients aged older than 70 years. The ESC considered it would be appropriate for the proposed restriction to be age agnostic.

3.6 The requested restriction is agnostic to Ph status. No evidence was presented supporting the use of blinatumomab in Ph positive patients in consolidation therapy. The PBAC previously considered the treatment effect of blinatumomab was unlikely to differ by Ph-status, and recommended both blinatumomab and inotuzumab ozogamicin for patients with Ph-positive relapsed/refractory B-ALL (para 5.3, Blinatumomab Public Summary Document, May 2019 PBAC meeting). The ESC considered it would be appropriate for the proposed restriction to be Ph-status agnostic.

3.7 The requested restriction is also broader than the available evidence for blinatumomab that was based on MRD directed treatment settings only. The role of blinatumomab in non-MRD directed treatment settings is unknown. The ESC advised that MRD testing is standard of care in Australian clinical practice. Hence, it would be highly unusual to treat this condition and not test for MRD.

3.8 The submission also proposed amendments to the relapsed/refractory PBS listing for the use of blinatumomab regardless of MRD status. The PBAC previously considered that it would be clinically appropriate to allow retreatment in the relapsed/refractory setting for patients who responded to blinatumomab in the MRD-positive setting (para 7.4, blinatumomab Public Summary Document (PSD), March 2019 PBAC meeting). No evidence was presented in the submission supporting the use of blinatumomab for retreatment following blinatumomab consolidation therapy for MRD-negative disease. The ESC considered that, consistent with the listing for MRD-positive patients, it would be appropriate to allow retreatment in the relapsed/refractory setting for patients who responded to blinatumomab in the MRD-negative setting.

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

4 Population and disease

4.1 Acute lymphoblastic leukaemia (ALL) is a rare, aggressive malignancy of the bone marrow, characterised by the proliferation of immature and abnormal lymphoid cells (lymphoblasts) in the bone marrow and peripheral blood. ALL is generally characterised by the emergence of haematological deficiencies, anaemia, thrombocytopenia, and neutropenia that give rise to the distinctive symptoms of fatigue, bruising, bleeding, enlarged lymph nodes, fever and infections. Hepatomegaly, splenomegaly, and lymphadenopathy may also be observed, as well

as symptoms related to central nervous system or testicular involvement (headache, weakness, seizures, vomiting, testicular enlargement).

4.2 The incidence of ALL is highest in children under 5 years of age, and peaks again in patients aged over 50 years. ALL may be related to either B-cell or T-cell precursors (with the majority identified as B-cell), and by genetic variant (Ph status).

4.3 Diagnosis by initial blood test is confirmed by bone marrow aspiration showing at least 20% lymphoblasts. Comprehensive morphological and cytogenetic testing is conducted to determine the extent, subtype, and genetic profile of the disease, as well as to identify suitable donors for stem cell transplantation (Jain 2013; Yeoh 2013). Molecular characterisation during diagnosis differentiates between a complex range of genetic abnormalities that can influence outcomes and response to targeted treatments (Inaba 2013). MRD is assessed following induction and consolidation chemotherapy for patients achieving complete haematological remission (CR), to determine risk stratification, treatment options and candidacy for allogeneic stem cell transplant (ASCT) and is a strong prognostic factor for risk of relapse.

4.4 The submission positioned blinatumomab as an add on to standard of care consolidation chemotherapy in patients achieving complete haematological remission who are MRD-positive or MRD-negative after induction chemotherapy, regardless of Ph expression.

4.5 The evaluation considered it was unclear if the combination blinatumomab and standard of care protocols used in the key clinical trial (E1910) will be preferred to standard of care chemotherapies currently used in the Australian setting, given the reported benefits and safety profile associated with blinatumomab in the clinical trial were impacted by the overall efficacy, tolerability and safety of the combined components. The Pre-Sub-Committee Response (PSCR) stated that Australian ALL experts have stated that they will not adopt the chemotherapy regimen used in E1910 as there is no evidence that it is superior and there are considerable risks associated with changing chemotherapy regimens.

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

5 Comparator

5.1 The submission nominated standard of care chemotherapy, with or without ASCT, as the main comparator. The ESC considered standard of care is an appropriate comparator.

5.2 The PBAC previously considered that standard of care chemotherapy was the appropriate comparator for blinatumomab in MRD-positive B-ALL, and that blinatumomab may be used in multiple discrete roles including as primary treatment, bridge to haematopoietic stem cell transplant (HSCT), optimisation of HSCT by eliminating MRD and treatment of molecular relapse (paragraphs 5.4, 5.5, 7.9, Blinatumomab PSD, July 2018 PBAC meeting).

5.3 The likely role of blinatumomab in the MRD-negative setting is uncertain given the key trial included ASCT as a randomisation stratification factor. The impact of blinatumomab on the use of subsequent therapies including ASCT is uncertain due to limited reporting in the trial.

5.4 The submission characterised standard of care as consolidation chemotherapy and subsequent treatments including ASCT, adjusted for age, prognostic risk factors and response to therapy.

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

6 Consideration of the evidence

Sponsor hearing

6.1 The sponsor requested a hearing for this item. The clinician discussed outcomes expected with current standard of care regimens noting the impact of age on event free survival (event free survival lower in patients ≥ 55 years of age for than younger patients). The clinician noted the standard of care regimen used in the E1910 study was different to standard of care chemotherapy regimens used in the Australian context but advised that they were broadly comparable and considered this was not an issue for the applicability of the E1910 clinical trial. The clinician also considered the treatment effect of blinatumomab was unlikely to differ by Ph-status, and addressed other matters in response to the Committee's questions. The PBAC considered that the hearing was informative as it provided a clinical perspective on treating this disease.

Consumer comments

6.2 The PBAC noted and welcomed the input from health care professionals (2) and organisations (2) via the Consumer Comments facility on the PBS website. The comments from health care professionals described the efficacy of blinatumomab as a frontline therapy in the treatment of B-ALL based on the E1910 trial. The input from health care professionals also described blinatumomab as less toxic than chemotherapy and noted that it can be delivered in an outpatient setting in the majority of cases. The comments also argued that the proposed blinatumomab listing should be age agnostic and requested access for patients for which the use of conventional chemotherapy is difficult (e.g. Down syndrome, hereditary cancer syndromes, immunodeficiency) or for patients with ALL who experience early onset, severe treatment related toxicity (such as severe fungal or bacterial infection). Input from the Leukaemia Foundation highlighted the need for new therapies due to the high mortality rate for patients with ALL and the highly toxic nature of existing treatments. The comments from the Australian & New Zealand Childrens Haematology/Oncology Group (ANZCHOG) highlight data suggesting a benefit of blinatumomab across age groups and advocate for children to also have access to

frontline therapy.

Clinical trials

6.3 The submission was based on one head-to-head trial comparing blinatumomab in combination with standard of care to standard of care alone, in patients with newly diagnosed Philadelphia chromosome-negative B-ALL in complete haematological remission who are MRD-negative or MRD-positive after initial induction chemotherapy (E1910).

6.4 Details of the trial presented in the submission are provided in Table 2.

Table 2: Trial and associated reports presented in the submission

Trial ID	Protocol title/Publication title	Publication citation
ECOG-ACRIN E1910	A phase 3 randomised trial of blinatumomab (IND# 117467, NSC# 765986) for newly diagnosed BCR-ABL negative B lineage acute lymphoblastic leukemia in adults.	Clinical Study Report: 18 October 2023.
	Litzow MR, et al. Consolidation therapy with blinatumomab improves overall survival in newly diagnosed adult patients with B-lineage acute lymphoblastic leukemia in measurable residual disease negative remission: results from the ECOG-ACRIN E1910 randomized phase 3 National Cooperative Clinical Trials Network trial.	*64th American Society of Hematology Annual Meeting and Exposition*; New Orleans, Louisiana, December 10-13, 2022; LBA-1 (abstract).
	Litzow MR, et al. Consolidation with blinatumomab improves overall and relapse-free survival in patients with newly diagnosed B-cell acute lymphoblastic leukemia: Impact of age and MRD level; ECOG-ACRIN E1910.	*28th Congress of the European Hematology Association*: Frankfurt, Germany, June 8-11, 2023; S115 (abstract).
	Luger SM, et al. Assessment of outcomes of consolidation therapy by number of cycles of blinatumomab received in newly diagnosed measurable residual disease negative patients with B-lineage acute lymphoblastic leukaemia in the ECOG-ACRIN E1910 randomised phase III National Clinical Trials Network trial.	*65th American Society of Hematology Annual Meeting and Exposition*; San Diego, California, December 9-12, 2023; 2877 (poster).

Source: Table 2-4 of the submission.

6.5 The key features of the E1910 trial are summarised in Table 3.

Table 3: Key features of the included evidence

Trial	N	Design/duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
Blinatumomab plus standard of care versus standard of care						
E1910	488	Phase 3, multicentre, open-label RCT. Median follow-up 4.5 years	High	Patients aged 30-70 years with newly diagnosed Philadelphia chromosome negative B-ALL	OS, RFS, (MRD-negative, MRD-positive and overall populations), adverse events	OS and RFS censored at on-protocol ASCT; OS and RFS after on-protocol ASCT

Source: Table 2-5, of the submission.

Abbreviations: ASCT, allogeneic stem cell transplant; MRD, measurable residual disease; OS, overall survival; RCT, randomised controlled trial; RFS, relapse-free survival.

6.6 The E1910 trial used a 4-step study design to identify eligible patients with B-ALL who achieve complete haematological remission after initial induction chemotherapy and induction intensification:

- Step 1 Induction (Arm A): all enrolled patients with newly diagnosed B-ALL aged 30-70 years with an ECOG performance status of 0-3 (N=488) assigned to receive induction chemotherapy. Patients who achieved complete haematological remission (CR) or complete remission with incomplete peripheral blood count recovery (CRi) progressed to Step 2.
- Step 2 Induction intensification (Arm B): all patients (N=333) assigned to receive induction intensification chemotherapy. Patients with an ECOG performance status of 0-2, who maintained CR/CRi progressed to Step 3.
- Step 3 Consolidation therapy (randomised treatment phase): all patients (N=286) were randomised to either blinatumomab plus standard of care chemotherapy (Arm C) or standard of care chemotherapy alone (Arm D), risk stratified by age (30 to <55 years vs ≥55 years), CD20 status, rituximab use, and intention for ASCT, in two cohorts (MRD-negative N=224; MRD-positive N=62).
- Step 4 Maintenance therapy (Arm E): All patients received 2.5 years of maintenance chemotherapy from the start of the Step 2 induction intensification phase.

6.7 The primary outcomes of the E1910 trial were conducted in the MRD-negative cohort, with the MRD-positive cohort and overall population analyses conducted as secondary outcomes.

6.8 The risk of bias in the MRD-negative population was high, given the open-label trial design, that could affect disease management decisions on the use of subsequent therapies (including ASCT) and reporting of treatment-related adverse events.

6.9 The E1910 trial protocol was amended 6 months after commencing (24 November 2014) to cease randomisation of patients with MRD-positive B-ALL to the standard of care comparator arm, following FDA approval of blinatumomab in the MRD-positive setting for children and adults. The risk of bias in the MRD-positive cohort is therefore high, and comparative analyses between treatment arms may not be reliable.

6.10 The trial included multiple randomisation stratification factors, including intent to receive ASCT (32% in the blinatumomab plus standard of care arm and 31% in the standard of care arm). Progression to ASCT was at clinician discretion. Only patients stratified at randomisation with intent to receive ASCT could progress to on-protocol ASCT. All other patients progressing to ASCT received off-protocol ASCT. Overall, fewer patients received on-protocol or off-protocol ASCT in the blinatumomab plus standard of care treatment arm (25.0%) compared to standard of care (29.5%) (22 on-protocol ASCT in each arm, 6 and 12 off-protocol ASCT in the blinatumomab and standard of care arms respectively). Fewer patients progressed to on-protocol or off-protocol ASCT than were identified by intent to receive ASCT at randomisation. The reasons for this difference are unknown due to the limited documentation on clinical criteria for progression to ASCT in the trial.

6.11 Off-protocol blinatumomab treatment was also reported in 19.6% of patients receiving standard of care but no off-protocol use was reported in the blinatumomab

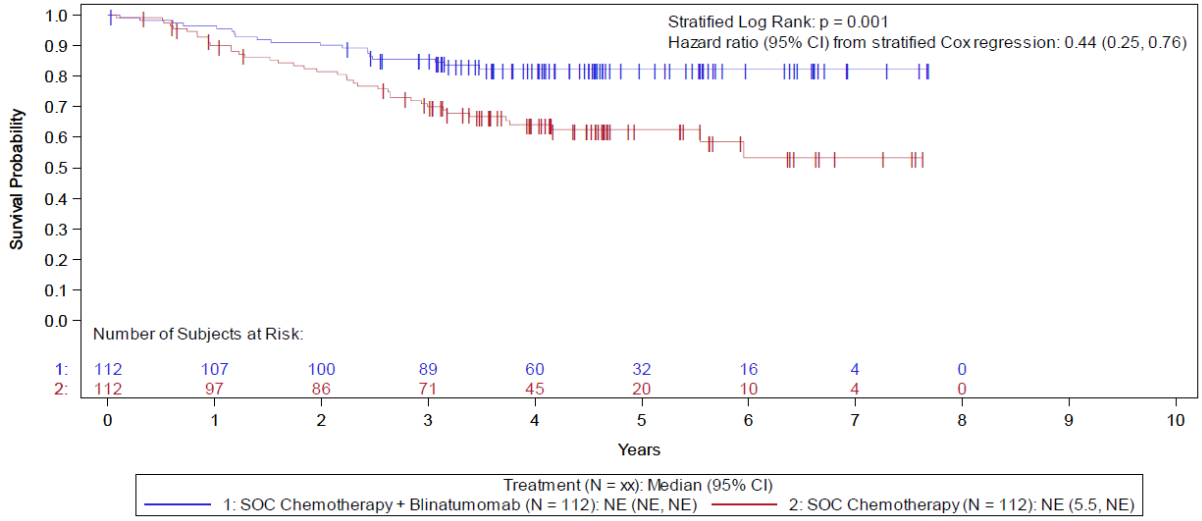
arm. The circumstances of off-protocol blinatumomab use was not reported in the trial. The impact of these differences on survival outcomes is uncertain.

Comparative effectiveness

MRD-negative cohort

6.12 The results for the primary outcome of the E1910 trial, overall survival in the MRD-negative cohort, are presented in Figure 1 and Table 4 below.

Figure 1: Kaplan-Meier for overall survival in MRD-negative patients in Trial E1910 (Step 3; FAS; cut-off 23 June 2023)



Source: Figure 2-3, of the submission.
Abbreviations: CI, confidence interval; FAS, full analysis set; MRD, measurable residual disease; NE, not estimable; SOC, standard of care.
Note: Censor indicated by vertical bar.

Table 4: Overall survival in MRD-negative patients in Trial E1910 (Step 3; FAS)

	Blinatumomab + standard of care N=112	**Standard of care N=112**
Median follow-up, years (95% CI)	4.5 (4.1, 4.6)	4.5 (4.0, 4.6)
Deaths, n (%) any cause	19 (17.0%)	40 (35.7%)
Censored, n (%) - Completed study without event - Continues on study - Discontinued study	93 (83.0%) 0 88 (78.6%) 5 (4.5%)	72 (64.3%) 0 64 (57.1%) 8 (7.1%)
Median time to censoring, years (95% CI)	4.5 (4.1, 4.6)	4.5 (4.0, 4.6)
Median overall survival, years (95% CI)	NE (NE, NE)	NE (5.5, NE)
Kaplan-Meier estimate, % (95% CI) - 0.5 years - 1 year - 2 years - 3 years - 4 years - 5 years - 6 years - 7 years	 98.2 (93.0, 99.5) 96.4 (90.7, 98.6) 90.1 (82.8, 94.4) 85.5 (77.5, 90.9) 82.4 (73.7, 88.4) 82.4 (73.7, 88.4) 82.4 (73.7, 88.4) 82.4 (73.7, 88.4)	 99.1 (93.8, 99.9) 90.0 (82.6, 94.3) 81.5 (72.8, 87.6) 70.0 (60.3, 77.7) 64.1 (53.9, 72.7) 62.5 (52.0, 71.3) 53.3 (37.8, 66.5) 53.3 (37.8, 66.5)
Hazard ratio (95% CI)[a]	**0.44 (0.25, 0.76)**	

Source: Table 2-17, of the submission.

Abbreviations: ASCT, allogeneic stem cell transplant; CI, confidence interval; FAS, full analysis set; MRD, measurable residual disease; NE, not estimable.

[a] Stratified by age (<55 years vs.≥55 years), CD20 status, rituximab use and intent to receive ASCT.

Note: Hazard ratio <1 indicates a lower average death rate and a longer survival for blinatumomab + standard of care compared to standard of care.

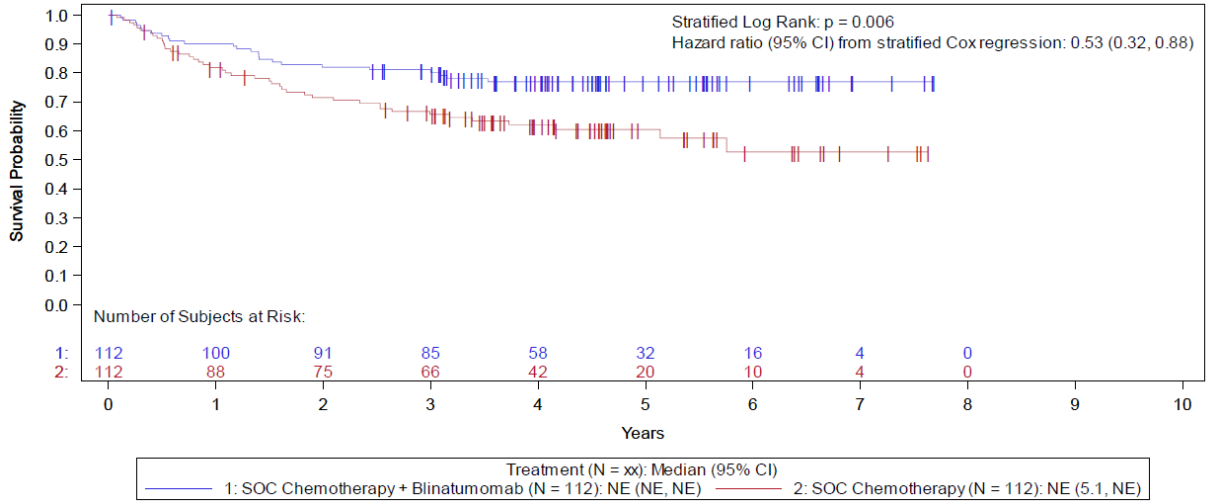
Bolded results were statistically significant

6.13 Median overall survival was not reached in either treatment arm. Overall survival was statistically significantly improved in the blinatumomab plus standard of care arm compared to the standard of care arm (HR = 0.44; 95% CI: 0.25, 0.76).

6.14 The trial included pre-specified subgroup analyses for overall survival in the MRD-negative cohort. Subgroup analyses by age showed a statistically significant treatment effect interaction (p=0.032), with patients aged ≥65 years treated with blinatumomab plus standard of care showing poorer outcomes in overall survival compared to standard of care patients, although patient numbers were small in the ≥65 year subgroup. A similar trend was observed in a subgroup analysis of patients aged <55 years (HR = 0.18; 95% CI: 0.06, 0.52) versus those aged ≥55 years (HR = 0.77; 95% CI: 0.37, 1.58), although a test for treatment effect interaction was not reported.

6.15 Figure 2 and Table 5 below present the results of relapse-free survival in the MRD-negative cohort of the E1910 trial.

Figure 2: Kaplan-Meier relapse free survival in MRD-negative patients in Trial E1910 (Step 3; FAS; cut-off 23 June 2023)



Source: Figure 2-4of the submission.
Abbreviations: CI, confidence interval; FAS, full analysis set; MRD, measurable residual disease; NE, not estimable; SOC, standard of care.
Note: Censor indicated by vertical bar.

Table 5: Relapse free survival in MRD-negative patients in Trial E1910 (Step 3; FAS)

	Blinatumomab + standard of care N=112	**Standard of care N=112**
Median follow-up, years (95% CI)	4.5 (4.1, 4.7)	4.5 (4.0, 4.6)
Events, n (%) - Relapse - Death due to any cause	25 (22.3%) 15 (13.4%) 10 (8.9%)	43 (38.4%) 32 (28.6%) 11 (9.8%)
Censored, n (%) - Relapse before start of RFS assessment - Completed study without event - Continues on study - Discontinued study	87 (77.7%) 0 0 84 (75.0%) 3 (2.7%)	69 (61.6%) 0 0 61 (54.5%) 8 (7.1%)
Median time to censoring, years (95%, CI)	4.5 (4.1, 4.7)	4.5 (4.0, 4.6)
Median time to event, years (95% CI)	NE (NE, NE)	NE (5.1, NE)
Kaplan-Meier estimate, % (95% CI) - 0.5 years - 1 year - 2 years - 3 years - 4 years - 5 years - 6 years - 7 years	 92.8 (86.1, 96.3) 90.1 (82.8, 94.4) 82.0 (73.5, 88.0) 81.1 (72.5, 87.2) 77.0 (67.8, 83.8) 77.0 (67.8, 83.8) 77.0 (67.8, 83.8) 77.0 (67.8, 83.8)	 91.9 (85.1, 95.7) 81.9 (73.4, 87.9) 71.5 (61.9, 79.0) 65.7 (55.9, 73.8) 62.1 (52.0, 70.7) 60.5 (50.1, 69.4) 52.7 (38.5, 65.0) 52.7 (38.5, 65.0)
Hazard ratio (95% CI)[a]	**0.53 (0.32, 0.88)**	

Source: Table 2-19 of the submission.
Abbreviations: ASCT, allogeneic stem cell transplant; CI, confidence interval; FAS, full analysis set; KM, Kaplan-Meier; MRD, measurable residual disease; NE, not estimable.
[a] Stratified by age (<55 years vs.≥55 years), CD20 status, rituximab use and intent to receive allogeneic SCT.
Note: Hazard ratio <1 indicates a lower average event rate and longer relapse-free survival for blinatumomab plus standard of care compared to standard of care.
Bolded results were statistically significant

6.16 Median relapse-free survival was not reached in either treatment arm. Relapse-free survival was statistically significantly improved in the blinatumomab plus standard of care arm compared to the standard of care arm (HR = 0.53; 95% CI: 0.32, 0.88).

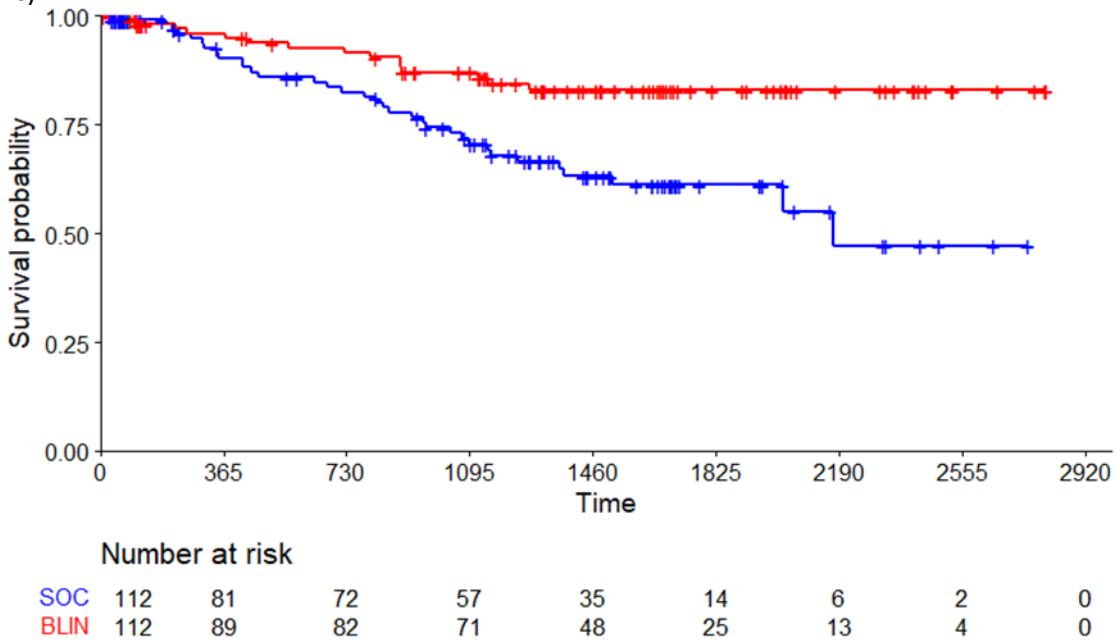
6.17 The submission argued that the absence of progression in the blinatumomab plus standard of care arm after a median of 4.5 years of follow up meets the current definition of cure in B-ALL (3 to 5 years of relapse-free survival is associated with a reasonable probability of cure, based on a Delphi panel of 13 clinicians from France, Germany, and the UK; Gidman et al, 2019). The submission considered that the lack of progression in both the overall survival and relapse free survival curves is suggestive of cure for a significant proportion of patients. The ESC agreed with the evaluation that the long-term survival outcomes and the magnitude of patients achieving cure is uncertain given the relatively small numbers of patients remaining at risk beyond 4.5 years in the trial.

6.18 Chemotherapy induction, induction intensification and consolidation therapy used in the E1910 trial were based on US regimens not commonly used in Australia. In addition, consolidation chemotherapy varied in intensity and uptake between treatment arms. Differences in standard of care chemotherapy between the E1910 and Australian clinical practice may impact the magnitude of benefit of blinatumomab in the Australian setting. The PSCR) stated that the chemotherapy regimens used in the US are more similar than they are different and are based on the fundamental principle of using multiple non-cross resistant agents. The PSCR noted the NCCN guidelines recommend several frontline regimens but don't suggest superiority of one regimen over another. The ESC agreed with the PSCR and considered that the differences in standard of care chemotherapy was not an issue for the applicability of the E1910 clinical trial.

6.19 The submission presented post hoc analyses of overall survival and relapse-free survival in the MRD-negative cohort of the E1910 trial based on outcomes censored at on-protocol ASCT and from on-protocol ASCT, used in the economic evaluation. It was unclear whether the analyses were based on the same data cut-off as the primary analysis (June 2023), and median follow-up was also not reported.

6.20 Figure 3 and Table 6 present results from the post hoc analysis of overall survival censored at on-protocol ASCT (E1910 trial Step 3 MRD-negative cohort).

Figure 3: Kaplan-Meier estimates of MRD-negative overall survival censored at on-protocol ASCT in trial E1910 (Step 3; FAS)



Source: Figure 3-7 of the submission.
Abbreviations: ASCT, allogeneic stem cell transplant; BLIN, blinatumomab; FAS, full analysis set; MRD, minimal residual disease; SOC, standard of care.

Table 6: MRD-negative overall survival censored at on-protocol ASCT in trial E1910 (Step 3; FAS)

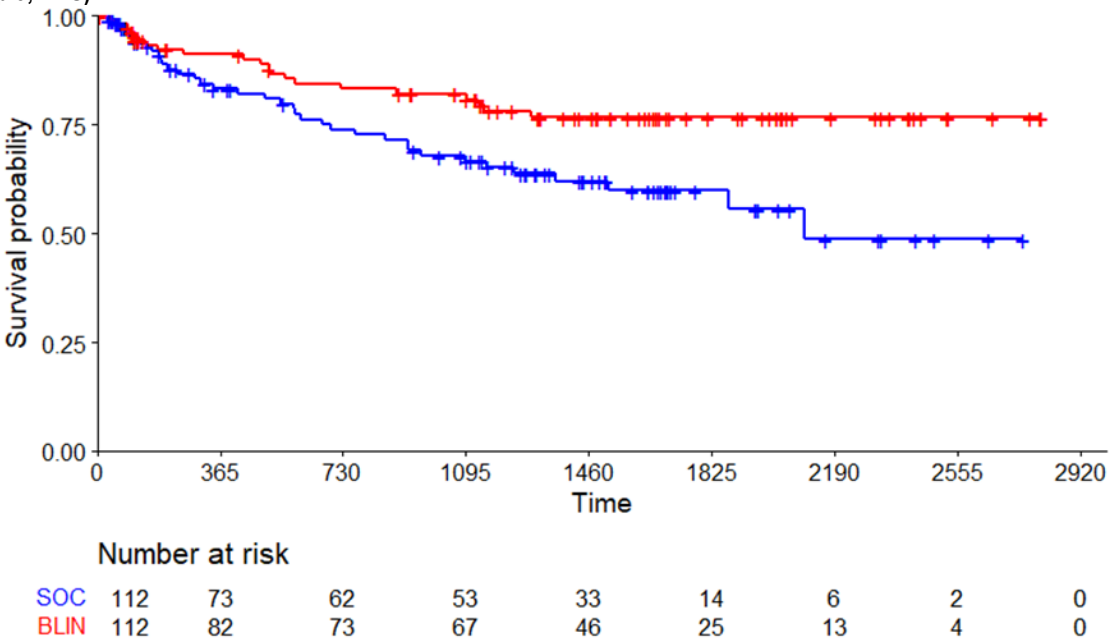
	Blin + SOC N=112	**SOC N=112**
Deaths, n (%) any cause	15 (13.4)	34 (30.4)
Censored, n (%)	97 (86.6)	78 (69.6)
- Received on-protocol ASCT	22 (19.6)	22 (19.6)
- Completed study without event	0	0
- Continuing study	92 (82.1)	73 (65.2)
- Discontinued study	5 (4.5)	5 (4.5)
Median time to censoring, years (95% CI)	4.0 (3.6, 4.5)	4.0 (3.6, 4.5)
Median overall survival, years (95% CI)	NE (NE, NE)	6.0 (5.5, NE)
Hazard ratio (95% CI) [a]	**0.44 (0.24, 0.82)**	

Source: Table 3-11of the submission.
Abbreviations: ASCT, allogeneic stem cell transplant; Blin, blinatumomab; CI, confidence interval; FAS, full analysis set; NE, not estimable; SOC, standard of care.
[a] Stratified by age (< 55 years vs ≥ 55 years), CD20 status, rituximab use, intent to receive allogeneic SCT

6.21 Median overall survival was not reached in the blinatumomab plus SOC treatment arm and was 6 years in the SOC treatment arm. The results of the analysis censored at on-protocol ASCT showed improved overall survival in the blinatumomab plus standard of care treatment arm compared to standard of care (HR = 0.44; 95% CI: 0.24, 0.82).

6.22 Figure 4 and Table 7 present results from the *post hoc* analysis of relapse-free survival censored at on-protocol ASCT (E1910 trial Step 3 MRD-negative cohort).

Figure 4: Kaplan-Meier estimates of MRD-negative relapse-free survival censored at on-protocol ASCT in trial E1910 (Step 3; FAS)



Source: Figure 3-9of the submission.
Abbreviations: ASCT, allogeneic stem cell transplant; BLIN, blinatumomab; FAS, full analysis set; MRD, minimal residual disease; SOC, standard of care.

Table 7: MRD-negative relapse-free survival censored at on-protocol ASCT in trial E1910 (Step 3; FAS)

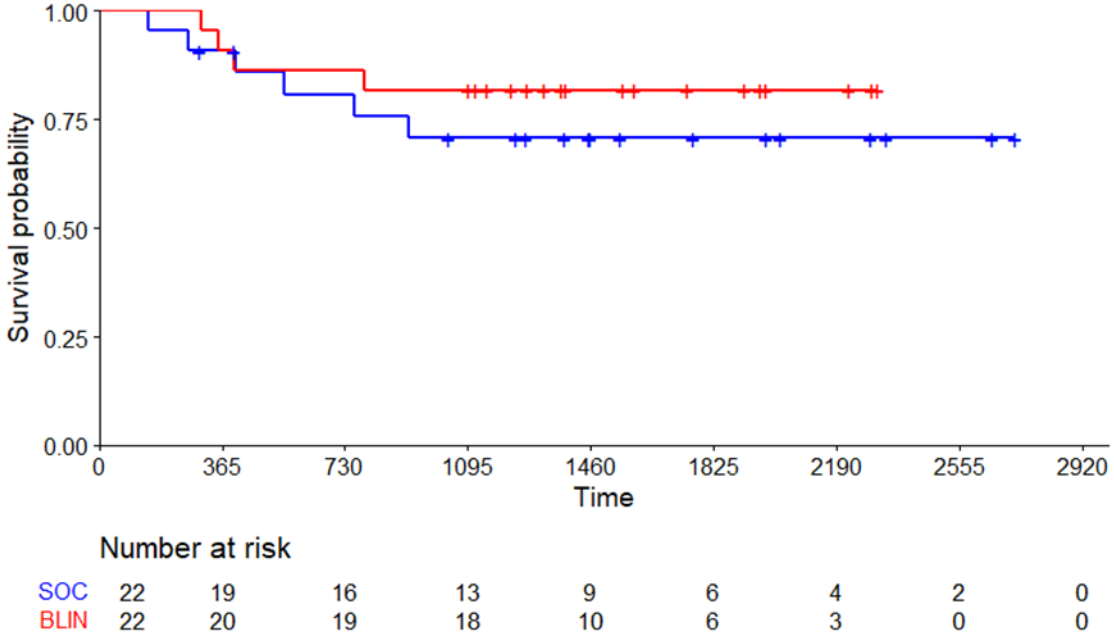
	Blin + SOC N=112	SOC N=112
Events, n (%)	21 (18.8)	36 (32.1)
- Relapse	13 (11.6)	27 (24.1)
- Deaths	8 (7.1)	9 (8.0)
Censored, n (%)	91 (81.3)	76 (67.9)
- Received on-protocol ASCT	22 (19.6)	22 (19.6)
- Completed study without event	0	0
- Continuing study	88 (78.6)	71 (63.4)
- Discontinued study	3 (2.7)	5 (4.5)
Median time to censoring, years (95% CI)	4.1 (3.6, 4.5)	4.0 (3.5, 4.5)
Median time to event, years (95% CI)	NE (NE, NE)	5.8 (4.2, NE)
Hazard ratio (95% CI) [a]	0.59 (0.34, 1.01)	

Source: Table 3-13of the submission.
Abbreviations: ASCT, allogeneic stem cell transplant; Blin, blinatumomab; CI, confidence interval; FAS, full analysis set; NE, not estimable; SOC, standard of care.
[a] Stratified by age (< 55 years vs ≥ 55 years), CD20 status, rituximab use, intent to receive ASCT.

6.23 Median relapse-free survival was not reached in the blinatumomab plus SOC treatment arm and was 5.8 years for SOC. There was no statistically significant difference in relapse-free survival between treatment arms, however the results favoured blinatumomab plus standard of care compared to standard of care.

6.24 Figure 5 and Table 8 present results from the *post hoc* analysis of overall survival from on-protocol ASCT (E1910 trial Step 3 MRD-negative cohort).

Figure 5: Kaplan-Meier estimates of MRD-negative overall survival from on-protocol ASCT in trial E1910 (Step 3; FAS)



Source: Figure 3-8 of the submission
Abbreviations: ASCT, allogeneic stem cell transplant; BLIN, blinatumomab; MRD, minimal residual disease; SOC, standard of care

Table 8: MRD-negative overall survival from on-protocol ASCT in trial E1910 (Step 3; FAS)

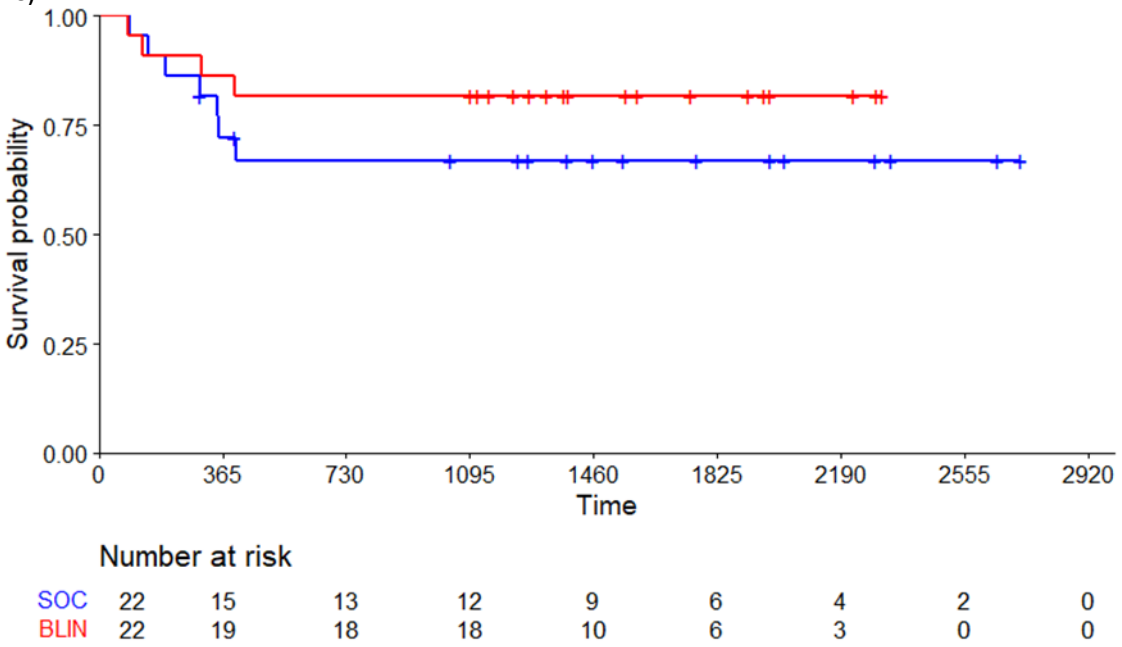
	Blin + SOC N=22	**SOC N=22**
Deaths, n (%)	4 (18.2)	6 (27.3)
Censored, n (%)	18 (81.8)	16 (72.7)
- Completed study without event	0	0
- Continuing study	18 (81.8)	13 (59.1)
- Discontinued study	0	3 (13.6)
Median overall survival, years (95% CI)	NE (NE, NE)	NE (NE, NE)
Median time to censoring, years (95% CI)	4.3 (3.6, 5.4)	4.2 (3.8, 6.4)
Hazard ratio (95% CI) [a]	0.73 (0.20, 2.65)	

Source: Table 3-12, of the submission.
Abbreviations: ASCT, allogeneic stem cell transplant; Blin, blinatumomab; CI, confidence interval; FAS, full analysis set; NA, not applicable; NE, not estimable; SOC, standard of care.
[a] Stratified by age (< 55 years vs ≥ 55 years), CD20 status (positive vs. negative vs not collected), rituximab use (yes vs no vs not collected), intent to receive allogeneic SCT (yes vs no)

6.25 Median overall survival was not reached in either treatment arm. There was no statistically significant difference between treatment arms, with few events occurring during the trial period.

6.26 Figure 6 and Table 9 present results from the *post hoc* analysis of relapse-free survival from on-protocol ASCT (E1910 trial Step 3 MRD-negative cohort).

Figure 6: Kaplan-Meier estimates of MRD-negative relapse-free survival from on-protocol ASCT in trial E1910 (Step 3; FAS)



Source: Figure 3-10, of the submission.
Abbreviations: ASCT, allogeneic stem cell transplant; BLIN, blinatumomab; FAS, full analysis set; MRD, minimal residual disease; SOC, standard of care.

Table 9: MRD-negative relapse-free survival from on-protocol ASCT in trial E1910 (Step 3; FAS)

	Blin + SOC N=22	SOC N=22
Events, n (%)	4 (18.2)	7 (31.8)
- Relapse	2 (9.1)	5 (22.7)
- Deaths	2 (9.1)	2 (9.1)
Censored, n (%)	18 (81.8)	15 (68.2)
- Completed study without event	0	0
- Continuing study	18 (81.8)	12 (54.5)
- Discontinued study	0	3 (13.6)
Median time to event, years (95% CI)	NE (NE, NE)	NE (1.1, NE)
Median time to censoring, years (95% CI)	4.3 (3.6, 5.4)	4.2 (3.5, 6.4)
Hazard ratio (95% CI) [a]	0.62 (0.18, 2.15)	

Source: Table 3-14of the submission.
Abbreviations: ASCT, allogeneic stem cell transplant; BLIN, blinatumomab; CI, confidence interval; FAS, full analysis set; NA, not applicable; NE, not estimable; NR, not reported; SOC, standard of care.
[a] Stratified by age (< 55 years vs ≥ 55 years), CD20 status, rituximab use, intent to receive allogeneic SCT.

6.27 Median relapse-free survival was not reached in either treatment arm. There was no statistically significant difference between treatment arms, with few events occurring during the trial period.

6.28 Table 10 summarises additional *post hoc* analyses conducted for the MRD-negative cohort of the E1910 trial, censored at on-protocol or off-protocol ASCT and from on-protocol or off-protocol ASCT.

Table 10: MRD-negative overall and relapse free survival by on-protocol or off-protocol ASCT in E1910 (Step 3; FAS)

	Blinatumomab + SOC n/N (%)	SOC n/N (%)	Hazard ratio[a] (95% CI)
Overall and relapse free survival censored at on-protocol or off-protocol ASCT (Step 3)			
Overall survival	13/112 (11.6%)	27/112 (24.1%)	**0.46 (0.24, 0.90)**
Relapse free survival	21/112 (18.8%)	34/112 (30.4%)	0.60 (0.34, 1.04)
Overall and relapse free survival from on-protocol or off-protocol ASCT (Step 3; patients receiving ASCT only)			
Overall survival	6/28 (21.4%)	13/33 (39.4%)	0.56 (0.21, 1.49)
Relapse free survival	4/25 (16.0%)	9/28 (32.1%)	0.46 (0.14, 1.52)

Source: Tables 2-17 and Tables 2-18of 'BLIN Evaluator Request 12 April 2024.docx'.

Abbreviations: ASCT, allogeneic stem cell transplant; CI, confidence interval; FAS, full analysis set; MRD, minimal residual disease; SOC, standard of care.

[a] Stratified by age (<55 years vs.≥55 years), CD20 status, rituximab use and intent to receive allogeneic SCT. Hazard ratio <1 indicates a lower average death rate and a longer survival for blinatumomab + SOC compared to SOC.

6.29 Results of the additional analysis censored at on-protocol or off-protocol ASCT showed similar results to the primary analysis, but showed no statistically significant difference between treatment arms for relapse free survival. Results of the additional analyses from on-protocol or off-protocol ASCT showed a similar trend favouring blinatumomab plus standard of care, but showed no statistically significant difference between treatment arms for overall survival or relapse free survival.

6.30 The submission noted that intention to ASCT was stratified at randomisation, and the proportion of MRD-negative patients who received on-protocol ASCT was the same in both treatment arms (19.6%). The submission and PSCR claimed that it was reasonable to assume that treatment effects observed in the primary outcomes of overall survival and relapse free survival in the E1910 trial were independent of ASCT. Overall, the ESC considered the comparative efficacy of blinatumomab plus standard of care versus standard of care alone among patients who progress to ASCT is uncertain given relatively few patients and events informing survival outcomes.

MRD-positive cohort

6.31 For the MRD-positive cohort, median overall survival was not reached in the blinatumomab plus standard of care arm and was 1.9 years in the standard of care arm. There were fewer deaths in the blinatumomab plus standard of care arm (27.5%) compared to the standard of care arm (59.1%), but the difference in overall survival did not reach statistical significance (HR = 0.40; 95% CI: 0.14, 1.12).

6.32 Similarly, median relapse free survival in the MRD-positive cohort was not reached in the blinatumomab plus standard of care arm and was 0.6 years in the standard of care arm. There were fewer relapse or death events in the blinatumomab plus standard of care arm (27.5%) compared to the standard of care arm (59.1%), but the difference in relapse-free survival did not reach statistical significance (HR = 0.37; 95% CI: 0.13, 1.03).

6.33 The evaluation and the ESC considered that the results for the MRD-positive cohort were affected by premature termination of randomisation and small sample size, and are not reliable.

Comparative harms

6.34 Table 11 summarises the proportions of patients reporting key adverse events in Step 3 of the E1910 trial in the MRD-negative cohort.

Table 11: Summary of key adverse events in the MRD-negative cohort of the E1910 trial (Step 3; SAS)

	Blinatumomab + standard of care N=111	Standard of care N=112
Any adverse events	111 (100%)	110 (98.2%)
Discontinuation due to adverse events	12 (10.7%)	5 (4.5%)
Grade ≥3 adverse event	109 (98.2%)	110 (98.2%)
Grade ≥4 adverse event	100 (90.1%)	106 (94.6%)
Death	3 (2.7%)	1 (0.9%)
Treatment-emergent adverse events of special interest		
Any TEAE of special interest	78 (70.3%)	43 (38.4%)
- Cytokine release syndrome	19 (17.1%)	0
- Neurologic events (Narrow)	72 (64.9%)	43 (38.4%)
Headache	46 (41.4%)	36 (32.1%)
Tremor	26 (23.4%)	5 (4.5%)
Aphasia	9 (8.1%)	0.0
Insomnia	9 (8.1%)	2 (1.8%)
Dizziness	8 (7.2%)	3 (2.7%)
Treatment-emergent expedited adverse events[a]		
Any expedited adverse event	67 (60.4%)	31 (27.7%)
- Febrile neutropenia	14 (12.6%)	14 (12.5%)
- Pyrexia	13 (11.7%)	1 (0.9%)
- Sepsis	13 (11.7%)	8 (7.1%)
- Device-related infection	11 (9.9%)	3 (2.7%)
- Neutrophil count decreased	9 (8.1%)	2 (1.8%)
- Alanine aminotransferase	9 (8.1%)	0.0
- Aphasia	8 (7.2%)	0.0
- Nausea	6 (5.4%)	0.0

Source: Table 12-2, p111, Table 12-5, Table 14-6.7.8, and Table 14-6.7.4, of the E1910 Clinical Study Report, Attachment 2.3 of the submission.

Abbreviations: AE, adverse event; MRD, measurable residual disease; NR, not reported; SAS, safety analysis set; TEAE, treatment-emergent adverse event.

[a] Adverse events that are both serious and unexpected are subject to expedited reporting.

6.35 The incidence of adverse events in the MRD-negative cohort was consistent with adverse events in the total trial population (including both MRD-negative and MRD-positive cohorts).

6.36 In the MRD-negative cohort, almost all patients in both treatment arms experienced an adverse event. There were 3 (2.7%) fatal adverse events reported in the blinatumomab plus standard of care treatment arm related to sepsis (n=2) and intracranial haemorrhage (n=1), and 1 (0.9%) fatal adverse event reported in the standard of care arm, related to sepsis. A higher proportion of patients in the blinatumomab plus standard of care arm discontinued treatment due to adverse events (10.7%) compared to the standard of care arm (4.5%).

6.37 Larger proportions of patients in the blinatumomab plus standard of care arm reported treatment-emergent adverse events of special interest (70.3%), including

cytokine release syndrome and neurological events, and serious and unexpected expedited adverse events (60.4%), including pyrexia, sepsis and device-related infection, compared to standard of care (38.4% and 27.7%, respectively).

6.38 The most frequently reported adverse events of Grade 3 or higher severity in the MRD-negative cohort were anaemia (blinatumomab plus standard of care 31.5% versus standard of care 41.1%), febrile neutropenia (20.7% versus 28.6%), sepsis (13.5% versus 9.8%), device-related infection (10.8% versus 5.4%), hyperglycaemia (10.8% versus 8.0%) and hypertension (10.8% versus 2.7%).

6.39 The submission presented data on potential safety concerns based on the Periodic Benefit-Risk Evaluation Report (PBRER) for the period from 3 December 2022 to 2 December 2023. Important identified risks included cytokine release syndrome, neurologic events, opportunistic infections, and medication errors. Important potential risks included haematopoietic stem cell transplantation related toxicity in children. Missing data included use in patients after recent ASCT, recent or concomitant treatment with other anti-cancer therapies (including radiotherapy), recent or concomitant treatment with other immunotherapy, long-term safety and efficacy, development impairment in children including neurological, endocrine, and immune system, subsequent relapse of leukaemia in children including in the central nervous system, long-term toxicity in children, and secondary malignant formation in children. No new safety signals were identified during the reporting period.

6.40 Safety data from 2 randomised, phase 3 clinical studies (20120215; AALL1331) investigating the use of blinatumomab compared to SOC chemotherapy in paediatric B-ALL patients in first relapse were also presented in the submission. Smaller proportions of Grade ≥3 adverse events were reported by paediatric patients treated with blinatumomab in the 20120215 (paediatric patients: 57.4%) and AALL1331 (adolescent and young adult patients: 84.6%) trials, compared to the E1910 trial MRD-negative cohort (98.2%), consistent with known differences in toxicity by age. Other safety data from the 20120215 and AALL1331 trials were generally consistent with the safety profile of blinatumomab in the E1910 trial, but showed higher proportions of patients reporting pyrexia (81.5%; 39.0%), nausea (40.7%; 28.0%), and anaemia (22.2%; 70.0%) in the 20120215 and AALL1331 trials, compared to the E1910 trial (11.7%, 5.4%, 31.5%).

Benefits/harms

6.41 On the basis of the direct evidence presented in the submission, after a median duration of follow-up of 4.5 years, for every 100 MRD-negative patients treated with blinatumomab plus standard of care compared to standard of care alone:

- Approximately 29 fewer patients would die over 7 years.
- Approximately 24 fewer patients would experience a relapse event (death or relapse) over 7 years.

- Approximately 32 additional patients would experience serious and unexpected adverse events including fever, infections, changes to markers of liver or kidney function and neurological adverse events.
- Approximately 17 additional patients would experience cytokine release syndrome (i.e. aggressive immune system response).
- Approximately 24 additional patients would experience neurological adverse events, including headache, tremor, aphasia (i.e. language difficulties), insomnia and dizziness.

Clinical claim

6.42 The submission described blinatumomab plus standard of care as superior in terms of effectiveness and non-inferior in terms of safety compared to standard of care alone. The evaluation considered the effectiveness claim was adequately supported by the clinical evidence presented, but the safety claim was not adequately supported.

6.43 The evaluation considered the following issues should be considered:

- The magnitude of effect observed in the E1910 trial was uncertain and benefits associated with blinatumomab in the E1910 trial may not be realised in the Australian setting.
  - Chemotherapy induction, induction intensification and consolidation therapy used in the E1910 trial were based on US regimens not commonly used in Australia. It is also unclear whether chemotherapy regimens in combination with blinatumomab based on the E1910 trial protocol will be preferred over standard of care regimens currently used in the Australian setting. The ESC considered that the differences in standard of care chemotherapy was not an issue for the applicability of the E1910 clinical trial (see paragraph 6.18).
  - The impact of potential differences in ASCT rates is uncertain due to the E1910 trial design that included intent to ASCT as a randomisation stratification factor and the limited reporting on the circumstances of progression to ASCT in the trial. The PSCR stated that intent to ASCT was included as a randomisation stratification factor because of the complexity of the patient journey in adult B-ALL and as multiple other factors (e.g. fitness, logistics, donor availability and patient choice) ultimately determine progression to ASCT. The PSCR stated that as the ASCT rate did not differ between the treatment arms, the magnitude of the blinatumomab treatment effect was not confounded by ASCT. The ESC considered the comparative efficacy of blinatumomab plus standard of care versus standard of care alone among patients who progress to ASCT is uncertain given relatively few patients and events informing survival outcomes.
  - The key trial excluded patients who were Ph positive, younger patients (less than 30 years of age) and older patients (aged above 70 years). The ESC

considered it was reasonable to assume that patients in these age groups and those who are Philadelphia chromosome positive would have similar outcomes to treatment with blinatumomab as those included in the E1910 trial.

- Long term survival benefits are uncertain given the median follow-up duration of 4.5 years in a trial population with a mean baseline age of 50 years. Survival outcomes were also subject to a high degree of censoring as most patients had yet to experience an event, and there were limited data on the use of subsequent therapies including ASCT, immunotherapies and chemotherapies that could affect disease trajectories.

- Safety outcomes indicated higher incidences of immunity related adverse events (e.g. cytokine release syndrome), infection (sepsis, device related infections), and nervous system related adverse events (headache, tremor, aphasia) in the blinatumomab plus standard of care arum compared to the standard of care arm of the key trial. The PSCR noted that although the safety profiles in each arm of the study were different, the overall rate and severity of adverse events was not. The ESC considered the adverse event profile from E1910 was consistent with the known safety profile of blinatumomab in other indications.

6.44 Overall, the ESC agreed with the evaluation that the effectiveness claim was adequately supported by the clinical evidence presented, but the safety claim was not adequately supported.

6.45 The PBAC considered that the claim of superior comparative effectiveness was reasonable.

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

Economic analysis

6.47 The submission presented a cost-utility analysis of blinatumomab in combination with standard of care consolidation chemotherapy compared to standard of care consolidation chemotherapy alone for the treatment of patients with B-ALL in complete haematological remission without minimal residual disease. The economic evaluation was based on E1910 trial data as well as other modelled variables.

Table 12: Summary of model structure, key inputs and rationale

Component	Description
Type of analysis	Cost-effectiveness/cost-utility analysis
Treatments	Blinatumomab in combination with SOC consolidation chemotherapy versus SOC consolidation chemotherapy alone
Outcomes	Life years and quality-adjusted life years
Time horizon	30 years in the model base case versus median follow-up of 4.5 years in the E1910 trial
Cycle length	2 weeks
Methods used to generate results	Partitioned survival analysis
Health states	Relapse-free no on-protocol ASCT, relapsed disease no on-protocol ASCT, dead no on-protocol ASCT, relapse-free after on-protocol ASCT, relapsed disease after on-protocol ASCT, dead after on-protocol ASCT
Health state distribution	The allocation of patients to the 6 mutually exclusive health states was informed by four survival curves: OS censored at on-protocol ASCT, RFS censored at on-protocol ASCT, OS after on-protocol ASCT and RFS after on-protocol ASCT. The implementation of these survival curves was staggered, with initial allocation to the no on-protocol ASCT health states followed by a forced distribution of 19.6% of patients (equal proportions in each arm) to the after on-protocol ASCT health states at fixed timepoints (16 weeks for blinatumomab and 8 weeks for SOC) based on time to on-protocol ASCT in the E1910 trial. Kaplan-Meier estimates for the two sets of OS and RFS curves were derived from a *post hoc* analysis of E1910 trial data and were used directly up to the extrapolation point of 4.5 years. Mixture cure models (weighted curves based on statistically cured and uncured fractions) were used to extrapolate each outcome to 30 years. Background mortality was informed by age- and sex-specific general population mortality estimates from the Australian Life Tables 2019-2021, assuming no excess mortality.
Utilities	Relapse-free states (no on-protocol ASCT and after on-protocol ASCT): 0.8534, relapsed disease states (no on-protocol ASCT and after on-protocol ASCT): 0.6920. Based on utilities included in previous submissions of blinatumomab in the MRD-positive setting (multi-step approach based on EQ-5D from the BLAST study propensity score analysis population, regression analysis of EQ-5D from the BLAST study, mapping of EORTC QLQ-C30 to EQ-5D from the TOWER trial, propensity score-adjusted regression analysis of EQ-5D from BLAST and TOWER studies). A treatment-related disutility of -0.57 for one year after receipt of on-protocol ASCT was applied (Sung 2003 and assumptions). No other treatment-related disutilities were included. The ESC noted that no adverse event disutilities were applied and considered this may not be reasonable given the clinical claim of non-inferior safety was inadequately supported in the submission.
Costs	Consolidation treatment and maintenance treatment costs based on trial-based circumstances of use of blinatumomab and consolidation chemotherapy. Frontline ASCT based on use of on-protocol ASCT in the trial with costs based on published estimates (Gordon 2009). Relapsed/refractory treatment costs based on off-protocol use of blinatumomab, ASCT and chemotherapy in the trial and assumptions. Disease management costs were based on expert advice and relevant MBS item fees. Adverse event costs were based on the incidence of adverse events in the trial with costs assuming events are hospitalised (relevant AR-DRGs using the NHCDC cost weights 2020-2021 Public Sector report). Terminal care costs based on published estimates (AIHW 2022 – last year of life: patterns in health service use and expenditure report).
Discounting	5% per year applied to costs and outcomes
Software package	Microsoft Excel

Source: Table 3-2 and Sections 3.2 to 3.6of the submission

Abbreviations: AIHW, Australian Institute of Health and Welfare; AR-DRG, Australian Refined Diagnosis Related Groups; ASCT, allogeneic stem cell transplant; NHCDC, National Hospital Cost Data Collection; OS, overall survival; QALY, quality adjusted life year; RFS, relapse-free survival; SOC, standard of care

6.48 The economic model is based on a partitioned survival analysis that uses a novel two-step (concurrent) structure to incorporate ASCT treatment pathways, which initially distributes all patients across 3 health states, relapse-free, relapsed and dead, followed by the subsequent addition of a further 3 states, relapse-free, relapsed and dead for the subset of patients who receive on-protocol ASCT. The concurrent estimation relied on the staggered implementation of four extrapolated survival curves: overall survival after on-protocol ASCT and censored at on-protocol ASCT; and relapse-free survival after on-protocol ASCT and censored at on-protocol ASCT.

6.49 The submission considered that on-protocol ASCT in the trial was a reasonable proxy for frontline ASCT, given the time to on-protocol ASCT estimates aligned with the recommended timing of frontline ASCTs in the trial (between 10 to 18 weeks of treatment in the blinatumomab arm; and between 0 to 14 weeks of treatment in the standard of care arm). The submission considered that the time to off-protocol ASCT estimates were longer and therefore more likely to reflect patients receiving ASCT in the relapsed/refractory setting. This assumption was inadequately justified given substantial variation in the time to off-protocol ASCT estimates and lack of data surrounding the circumstances of use of off-protocol ASCT, particularly in relation to disease status.

6.50 All patients who received on-protocol ASCT were assumed to receive it in Week 16 in the blinatumomab arm and in Week 8 in the standard of care arm. Survival estimates were weighted from these timepoints, based on 80.4% with no on-protocol ASCT and 19.6% with on-protocol ASCT in the trial (equal between arms). The assumed fixed timing of ASCT lacked face validity but may be necessary given the model was unable to track the occurrence of events at any given time. The ESC agreed with the evaluation that the fixed timing of ASCT was unlikely to reflect clinical practice.

6.51 The PSCR noted that the PBAC had previously considered the absence of ASCT health states in the March 2019 model of blinatumomab in MRD-positive B-ALL did not adequately reflect the treatment pathways. The PSCR stated that based on this advice the model structure was chosen to explicitly include ASCT health states. The ESC considered the stepwise incorporation of ASCT health states did not address key structural limitations associated with a partitioned survival analysis, particularly the inability to track events and lack of explicit links between treatments received, disease status and mortality.

6.52 The ESC noted the model structure also limited the ability to appropriately incorporate costs and consequences associated with subsequent anti-cancer treatments for relapsed/refractory disease. The attribution of costs required assumptions that lacked face validity (see Table 13 below) and there was no transparency regarding likely changes in disease trajectory that would have impacts on both survival and quality of life. The ESC considered the use of an alternative model structure (e.g. Markov state transition) would be a more robust approach given events could be tracked and treatments could be explicitly linked with subsequent health states and survival

outcomes. This approach would also provide greater transparency and the ability to test underlying assumptions in sensitivity analyses.

6.53 The difference in total cost between arms was primarily driven by blinatumomab drug costs, partially offset by the reduced use of relapsed/refractory treatments. The cost of frontline ASCT had no impact on the economic analysis given the costs were applied upfront to identical proportions of patients in each arm. As noted above, the ESC considered that this was unlikely to represent clinical practice.

6.54 The difference in health outcomes between treatment arms was primarily driven by improved survival in patients who were relapse-free and did not receive on-protocol ASCT in the blinatumomab arm.

6.55 Key drivers of the economic model are summarised in Table 13.

Table 13: Key drivers of the model

Description	Method/Value	Impact
Model structure	The incorporation of ASCT health states within a partitioned survival analysis was complex and did not appear to be informative of the costs and consequences associated with alternative treatment pathways. The evaluation considered it would be more appropriate to consider Markov state transition or microsimulation models given their ability to track events and explicitly link treatments received with disease status and survival outcomes. The PSCR stated that the survival benefits in the model are driven by the magnitude and duration of survival benefits observed in the E1910 trial, stratified by ASCT. As such, the PSCR argued that each of these model types is likely to generate comparable results given the use of the same trial data to generate assumptions regarding the extrapolation of long-term outcomes. The ESC agreed with the evaluation that a Markov state transition model structure would be a more robust approach that would provide greater transparency and the ability to test underlying assumptions in sensitivity analyses.	Unclear
Extrapolated survival benefit	The clinical plausibility of extrapolated survival benefits based on mixture cure models was uncertain. The clinical plausibility of modelled survival benefits is discussed further under Figure 8 below. The assumption that statistically cured patients have no excess mortality appears optimistic given some of these patients are likely to experience long-term disease-related and/or treatment-related complications. The trial data indicated that some patients would have received multiple lines of therapy including chemotherapy for up to 3 years and/or allogeneic stem cell transplant and other immunotherapies.	High, favours blinatumomab
Health state utilities	The validity of the utility estimates (0.8534 relapse-free, 0.6920 relapsed disease) could not be determined due to poor documentation on the derivation of these values based on previous blinatumomab submissions for the MRD-positive setting (based on EQ-5D from BLAST propensity score analysis population, regression analysis of EQ-5D from BLAST, mapping of EORTC QLQ-C30 to EQ-5D from TOWER, propensity score-adjusted regression analysis of EQ-5D from BLAST and TOWER) and limited discussion on the applicability of these estimates to the current model. The PBAC previously considered that the utility estimates were not adequately justified and unlikely to have been conservative (para 7.13, blinatumomab PSD, March 2019 PBAC meeting).	Moderate, favours blinatumomab

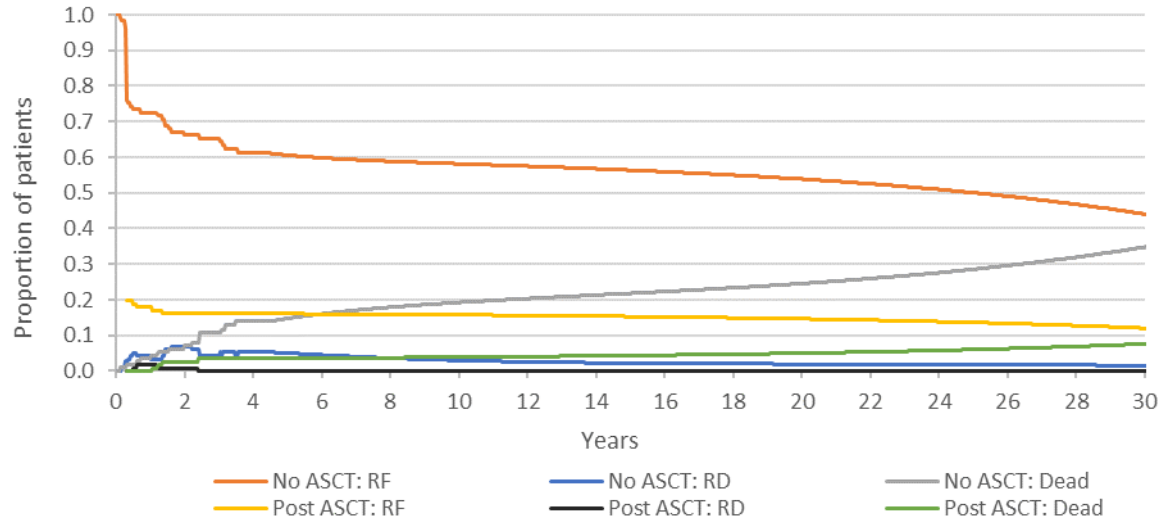
Description	Method/Value	Impact
	The use of a higher utility estimate for relapse-free disease in MRD-negative patients (estimated as 0.8534) compared to MRD-positive patients (0.806) was also reliant on the assumption that MRD response is associated with improved quality of life, which was inadequately justified. The estimate for MRD-negative patients appeared optimistic as it exceeds published EQ-5D-3L estimates in the Australian general population (0.85 from age 45 years declining to 0.80 from age 75 years; reported in Clemens 2014). The PSCR stated that the utility value applied for the relapse-free state was slightly higher than the value used in the MRD-positive submission as this was a function of the two disease states and is based on the available data from the BLAST trial. The PSCR stated that an updated literature search did not identify any other utility values. The ESC agreed with the evaluation that the use of a higher utility estimate for relapse-free disease in MRD-negative patients was inadequately justified. Instead, the ESC considered the utility estimate for relapse-free disease in MRD-positive patients (0.806) should be applied to MRD-negative patients in the relapse-free disease health state. The pre-PBAC response applied a utility of 0.806 to MRD-negative patients in the relapse-free disease health state in a revised base case.	
Relapsed/refractory treatment costs	Relapsed/refractory treatment costs were based on the weighted cost of the most commonly used off-protocol treatments in the standard of care arm of the E1910 trial (68.8% blinatumomab, 46.9% ASCT, 18.8% chemotherapy) applied to an estimated proportion of patients who experience relapse in the model. The submission acknowledged that the model does not explicitly track the occurrence of events and that the partitioned survival analysis is unable to differentiate between deaths in patients who are relapse-free and those who experienced relapse. Therefore, the submission used the distribution of events (i.e. relapses versus deaths) reported for relapse-free survival in the whole MRD-negative cohort in the trial, assuming that all relapse events were treated (60% blinatumomab, 74.4% standard of care). Modelled relapsed/refractory treatment costs were highly uncertain due to the following issues: • The submission noted that the assumed use of blinatumomab as subsequent treatment in the blinatumomab arm was inconsistent with the trial but claimed that the approach was conservative given the addition of blinatumomab treatment costs with no change to modelled outcomes. The approach assumes no impact on the choice of subsequent treatments following earlier use of blinatumomab (including the use of blinatumomab for relapsed/refractory disease). • The approach inappropriately assumes that off-protocol treatment use in the trial was representative of treatments used in the relapsed/refractory setting. • The approach assumes the same relapsed/refractory treatments are used despite receipt of on-protocol ASCT. The application of the same uptake rates effectively assumes that 47% of patients who relapse after ASCT would undergo ASCT again, which does not meet face validity. • The cost of blinatumomab was based on 53 vials, which appears to be based on the cost of blinatumomab in the MRD-positive setting, rather than 42 vials for relapsed/refractory disease (Table 3, blinatumomab PSD, July 2019 PBAC meeting). • Drug and hospitalisation costs associated with relapsed/refractory chemotherapy were incorrectly estimated in the submission using the ALLG ALL06 protocol for consolidation chemotherapy (following induction chemotherapy) rather than salvage chemotherapy for recurrent disease. • ASCT costs were based on a relatively old study (Gordon 2009) and may not be representative of current practice. The submission's inflation adjustment	Moderate, direction unclear

Description	Method/Value	Impact
	was inappropriate. • The application of the weighted cost effectively distributes the full cost of all treatments in a single model cycle irrespective of time on treatment or treatment modality.	

Source: constructed during the evaluation based on Section 3and the blinatumomab economic model of the submission
Abbreviations: ASCT, allogeneic stem cell transplant; MRD, minimal residual disease

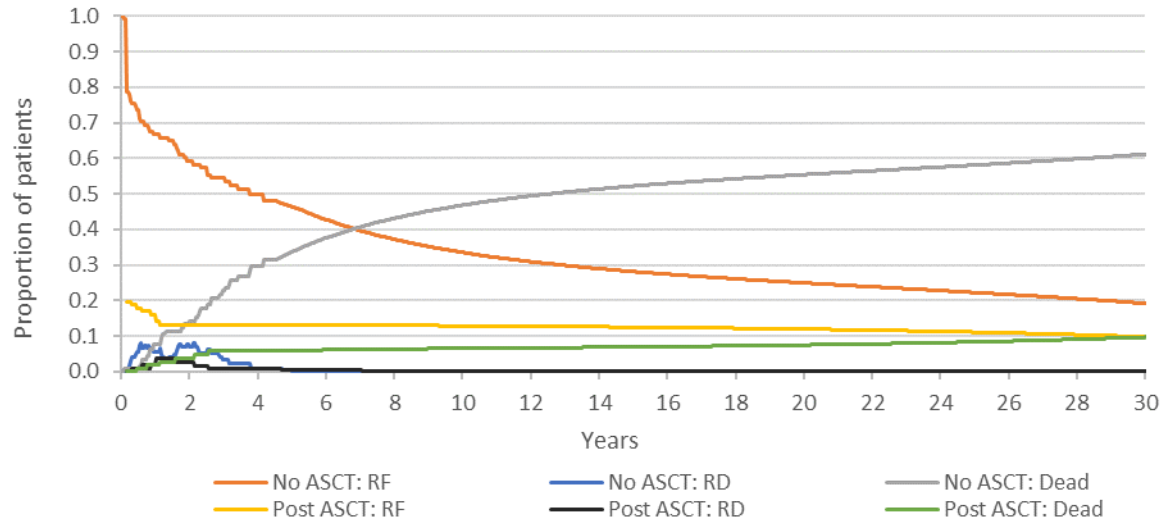
6.56 Figure 7 and Figure 8 present the model traces for the blinatumomab and standard of care arms, respectively.

Figure 7: Model trace for the blinatumomab arm



Source: Figure 3-26 of the submission
Abbreviations: ASCT, allogeneic stem cell transplant; RD, relapsed disease; RF, relapse-free

Figure 8: Model trace for the standard of care arm



Source: Figure 3-27 of the submission
Abbreviations: ASCT, allogeneic stem cell transplant; RD, relapsed disease; RF, relapse-free

6.57 The model traces show the impact of the concurrent structure, with forced allocations of patients from the relapse-free no on-protocol ASCT state to the relapse-free after

on-protocol ASCT state at fixed timepoints (16 weeks in blinatumomab and 8 weeks in standard of care).

6.58 The traces also show a modelled survival benefit for blinatumomab versus standard of care over the median follow-up period of the trial of 4.5 years, persisting throughout the 30-year model duration. Survival benefits are largely driven by patients who are in the relapse-free no on-protocol ASCT health state, although there were also survival gains associated with patients who are relapse-free after on-protocol ASCT.

6.59 The relapsed disease traces show a modelled benefit in favour of blinatumomab, with fewer patients experiencing disease relapse compared to standard of care. The predicted estimates for relapsed patients in the blinatumomab arm showed an unexpected pattern (shown in the blue line of Figure 7), where these patients appear to experience relatively low rates of mortality over the modelled duration. The reason for this could not be determined during the evaluation.

6.60 The submission claimed that the plateaus at the tail-end of Kaplan-Meier curves for overall survival and relapse-free survival were indicative of cure in a significant proportion of patients who received frontline therapy in the trial (see Figure 1 and Figure 2). There is known potential for cure with frontline treatment. However, the evaluation and the ESC considered that the likely proportion who achieve cure based on the trial data is uncertain given the high degree of censoring and limited data regarding the circumstances of use of subsequent therapies (e.g. it was unclear if the outcomes in the standard of care arm adequately accounted for the efficacy of later-line treatments such as access to blinatumomab or ASCT in the relapsed/refractory setting).

6.61 The difference in health outcomes between arms was driven by assumptions of cure and long-term survival benefit that were separately modelled, based on receipt of on-protocol ASCT in the trial. During the evaluation, the probabilities of death in each arm were compared with background mortality to determine approximate cure rates and cure timepoints in the model.

6.62 An approximate cure timepoint was estimated in each arm based on a mortality difference of less than 0.01% between background mortality and modelled estimates. For modelled overall survival censored at on-protocol ASCT, the cure timepoint was approximately 12 years for blinatumomab (75% of surviving patients) and 29 years for standard of care (25% of surviving patients). For modelled overall survival after on-protocol ASCT, the cure timepoint was approximately 2.2 years in the blinatumomab arm (82% of surviving patients) and from 8.4 years in the standard of care arm (67% of surviving patients).

6.63 Overall, the ESC agreed with the evaluation that incorporation of on-protocol ASCT health states within a partitioned survival analysis and use of mixture cure models for extrapolation introduced additional complexity and difficulty in determining the validity of modelled outcomes.

6.64 The results of the stepped economic evaluation are presented in Table 14 below.

Table 14: Results of the stepped economic evaluation

Step and component	BLIN	SOC	Increment
Step 1: 5-year time horizon, trial-based outcomes [a], consolidation treatment costs (drug acquisition, administration), frontline ASCT costs, 5% discounting to costs and outcomes			
Costs	$	$35,567	$
LYs	4.044	3.574	0.470
Incremental cost per LY gained			$ [1]
Step 2: Add utility values			
Costs	$	$35,567	$
LYs	4.044	3.574	0.470
QALYs	3.318	2.922	0.396
Incremental cost per QALY gained			[2]
Step 3: Extrapolate to 30-year time horizon			
Costs [b]	$	$35,567	$
LYs	12.537	8.541	3.997
QALYs	10.516	7.156	3.360
Incremental cost per QALY gained			[3]
Step 4: Add costs associated with maintenance treatment, relapsed/refractory treatment, disease management, adverse events and terminal care			
Costs	$	$113,366	$
LYs	12.537	8.541	3.997
QALYs	10.516	7.156	3.360
Incremental cost per QALY gained (base case)			[4]

Source: Table 3-56, of the submission

Abbreviations: ASCT, allogeneic stem cell transplant; BLIN, blinatumomab; LY, life year; QALY, quality-adjusted life year; SOC, standard of care

[a] Kaplan-Meier estimates from a *post hoc* analysis of survival outcomes (overall survival, relapse-free survival) censored at on-protocol ASCT and from ASCT applied for 4.5 years, then extrapolated using mixture cure models to 5 years

[b] There were no changes to the costs in each arm as costs associated with consolidation treatment and frontline ASCT were applied as one-off upfront costs in the model (already included in Step 1 of the analysis)

The redacted values correspond to the following ranges

1 $355,000 to < $455,000

2 $455,000 to < $555,000

3 $55,000 to < $75,000

4 $45,000 to < $55,000

6.65 The extrapolation of the modelled time horizon to 30 years had the largest impact on the stepped economic evaluation. The ESC, noting that the time horizon was consistent with the economic evaluation of blinatumomab in the MRD-positive setting recommended by the PBAC in July 2019, considered the 30 year time horizon reasonable; however, the ESC did note that the 30 year time horizon introduced uncertainty as there was considerable extrapolation of the trial data (median follow-up of 4.5 years). In the current economic model, 88% of incremental QALYs and 2% of incremental costs were accrued in the extrapolated period beyond 5 years.

6.66 Based on the economic model, treatment with blinatumomab in combination with standard of care consolidation chemotherapy was associated with a cost per QALY gained of $45,000 to < $55,000 compared to standard of care consolidation chemotherapy for the treatment of patients with B-ALL in haematological complete remission who are MRD-negative following induction chemotherapy.

6.67 For every patient treated with blinatumomab in combination with standard of care versus standard of care and followed up for 30 years, the economic model (without discounting) estimated that there would be:

Additional consolidation treatment costs (drug acquisition, administration) of $[redacted], additional adverse event costs of $[redacted], additional maintenance treatment costs of $[redacted], additional disease management costs of $[redacted] and no difference in frontline ASCT costs.

Reduced costs of subsequent therapies for relapsed/refractory disease of $[redacted].

- An additional 8.29 years of life lived and an additional 6.98 quality-adjusted life years.

6.68 The results of key sensitivity analyses are summarised in Table 15.

Table 15: Sensitivity analyses

Analysis	Incremental cost ($)	Incremental QALY	ICER	% change
Base case	[redacted]	**3.3595**	[redacted][1]	**-**
Discount rate (base case 5% costs and outcomes)				
0%	[redacted]	6.9776	[redacted][2]	-[redacted]%
3.5%	[redacted]	4.1084	[redacted][3]	-[redacted]%
Time horizon (base case 30 years)				
5 years	[redacted]	0.3959	[redacted][4]	+[redacted]%
10 years	[redacted]	1.1787	[redacted][5]	+[redacted]%
20 years	[redacted]	2.5401	[redacted][6]	+[redacted]%
Overall survival extrapolation (base case OS censored at on-protocol ASCT: blinatumomab exponential MCM, SOC loglogistic MCM; OS from on-protocol ASCT: blinatumomab lognormal MCM, SOC exponential MCM)				
SOC censored at ASCT: exponential MCM	[redacted]	4.3370	[redacted][3]	-[redacted]%
SOC censored at ASCT: generalised gamma MCM	[redacted]	3.1976	[redacted][1]	+[redacted]%
SOC censored at ASCT: Gompertz MCM	[redacted]	3.0085	[redacted][6]	+[redacted]%
SOC censored at ASCT: lognormal MCM	[redacted]	3.8205	[redacted][3]	-[redacted]%
SOC censored at ASCT: Weibull MCM	[redacted]	2.9043	[redacted][6]	+[redacted]%
Overall survival curve convergence (base case no convergence)				
Linear convergence from 4.5 years to 30 years	[redacted]	2.0734	[redacted][7]	+[redacted]%
Linear convergence from 10 years to 30 years	[redacted]	2.4052	[redacted][6]	+[redacted]%
Health state utilities (base case relapse-free 0.8534, relapsed disease 0.6920; first year post ASCT: 0.2834)				
Relapse-free 0.80	[redacted]	3.1618	[redacted][1]	+[redacted]%
Relapse-free 0.70	[redacted]	2.7914	[redacted][6]	+[redacted]%
Relapse-free 0.806 (based on MRD-positive B-ALL submission)	[redacted]	*3.2025*	[redacted][1]	+[redacted]%
Relapsed disease 0.60	[redacted]	3.3334	[redacted][1]	+[redacted]%
Relapsed disease 0.80	[redacted]	3.3902	[redacted][1]	-[redacted]%
First year post ASCT 0.40	[redacted]	3.3606	[redacted][1]	[redacted]%
First year post ASCT 0.20	[redacted]	3.3587	[redacted][1]	[redacted]%
Blinatumomab consolidation treatment costs (base case $[redacted] based on 82.6 treatment days including drug costs, hospitalisation, bag changes and infusion pump costs)				
101 treatment days (assumed based on treatment protocol) [a]	[redacted]	3.3595	[redacted][6]	+[redacted]%
75.03 treatment days (excluding wastage, based on mean volume of blinatumomab received)	[redacted]	3.3595	[redacted][3]	-[redacted]%
Hospitalisation cost $6,676 per treatment cycle [b]	[redacted]	3.3595	[redacted][1]	+[redacted]%

Analysis	Incremental cost ($)	Incremental QALY	ICER	% change
Relapsed/refractory treatment costs (base case weighted cost of $[redacted] based on costs of blinatumomab, ASCT and chemotherapy, applied to 60% of relapsed events for blinatumomab and 74.4% of relapsed events for SOC during the first 4.5 years of the model)				
Reduced blinatumomab treatment costs based on 42 treatment days (total drug, hospitalisation, bag change, infusion pump costs of $[redacted])	[redacted]	3.3595	[redacted][1]	+[redacted]%
Reduce ASCT costs to $127,930		3.3595	[redacted][1]	+[redacted]%
Weighted cost of $[redacted] in the blinatumomab arm based on off-protocol use of ASCT (40%), chemotherapy (6.7%) and no blinatumomab (0%) in the trial		3.3595	[redacted][1]	-[redacted]%
No relapsed/refractory treatment costs		3.3595	[redacted][6]	+[redacted]%
Weighted cost applied to equal proportions of relapsed events in both arms (74.4%)		3.3595	[redacted][1]	+[redacted]%
Weighted cost applied to relapsed events (60% blinatumomab, 74.4% SOC) throughout the model		3.3595	[redacted][1]	-[redacted]%
Weighted cost applied to relapsed events from 4.5 years onwards (25% blinatumomab, 25% SOC)		3.3595	[redacted][1]	-[redacted]%
Effective AEMP per vial (base case: $[redacted])				
Effective AEMP per vial $[redacted], based on price for MRD-positive B-ALL	[redacted]	3.3595	[redacted][1]	-[redacted]%
Multivariate analyses				
$[redacted] per vial; relapse-free utility 0.806; OS linear convergence from 4.5 to 30 years	[redacted]	1.9817	[redacted][7]	+[redacted]%
$[redacted] per vial; relapse-free utility 0.806; OS linear convergence from 10 to 30 years		2.2950	[redacted][6]	+[redacted]%

Source: Section 3.9, and the blinatumomab economic model of the submission

Abbreviations: ASCT, allogeneic stem cell transplant; ICER, incremental cost-effectiveness ratio; MCM, mixture cure model; NHCDC, National Hospital Cost Data Collection; OS, overall survival; QALY, quality adjusted life year; RR, relative risk; SOC, standard of care

[a] Assuming all patients who do not receive on-protocol ASCT receive 4 cycles of blinatumomab and all patients who receive on-protocol ASCT receive 2 cycles of blinatumomab

[b] Based on a cost per admission of $8,006 for 3.1 days minus $1,330 in pharmacy costs (AR-DRG 60B; NHCDC 2020-21 Public Sector report, acute cost weights AR-DRG v10.0)

The redacted values correspond to the following ranges

1 $45,000 to < $55,000
2 $15,000 to < $25,000
3 $35,000 to < $45,000
4 $355,000 to < $455,000
5 $135,000 to < $155,000
6 $55,000 to < $75,000
7 $75,000 to < $95,000

6.69 The model was most sensitive to the time horizon, extrapolated survival benefit, the discount rate and the cost of consolidation treatment with blinatumomab. Alternative health state utilities and relapsed/refractory treatment costs had moderate impacts on the ICER per QALY gained.

6.70 The magnitude of extrapolated survival benefit appeared most sensitive to the use of alternative mixture cure models for overall survival censored at on-protocol ASCT in the standard of care arm. The ESC considered this is likely due to sparseness of data informing the tail end of Kaplan-Meier estimates in the standard of care arm, with fewer patients remaining at risk at later timepoints in the trial compared to the blinatumomab arm.

6.71 The model includes curve convergence functionality to test the impact of overall survival convergence over time. While the model is sensitive to assumptions of linear convergence, the submission argued that the assumptions are inappropriate given the potential for cure with frontline treatment of B-ALL. The ESC considered the long-term survival benefits of blinatumomab in the MRD-negative setting are uncertain given the median follow-up duration of 4.5 years, the high degree of censoring of survival outcomes (as most patients had yet to experience an event), and the limited data on the use of subsequent therapies that could affect disease trajectories (see paragraph 6.60). As such, ESC considered that it would be more appropriate for the overall survival curves to converge linearly between 10 and 30 years. The pre-PBAC response agreed to the application of curve convergence between 10 and 30 years.

6.72 The impact of blinatumomab on ASCT rates is uncertain due to limitations with the trial design (planned ASCT was a randomisation factor). However, the ability to adequately test alternative assumptions regarding ASCT rates in the model was also limited by the partitioned survival design.

6.73 Due to structural limitations, changes to the utilisation of relapsed/refractory treatments only affected modelled costs without affecting survival endpoints or quality of life. There were additional uncertainties associated with the implementation of these costs as the model structure is unable to track the occurrence of events and/or patient status at any given time.

6.74 The ESC noted the effective AEMP per vial for blinatumomab used in the base case of the economic model was higher than the current AEMP in the MRD-positive setting (see paragraph 3.2). The ESC further noted that the treatment duration is longer in MRD-negative versus MRD-positive patients (average of 83 vials versus 53 vials), and that the cost offsets are higher in MRD-positive due to reduced use of blinatumomab in the relapse/refractory setting. The ESC considered, in the context of the clinical trial results, that the additional modelled incremental QALYs in the MRD negative setting versus the MRD positive setting (3.36 vs 1.19) used to justify the increased cost for blinatumomab in the MRD negative setting to be uncertain. The pre-PBAC response offered a blinatumomab ex-manufacturer price consistent with the current AEMP in the MRD-positive setting (see paragraph 3.2).

6.75 The submission presented a simplified 3-state partitioned survival analysis (including relapse-free, relapsed disease and dead states) in sensitivity analyses based on key endpoints of overall survival and relapse-free survival in the trial (without censoring for on-protocol ASCT), extrapolated over time using mixture cure models. The results were sensitive to alternative mixture cure models used to extrapolate overall survival, with the ICER per QALY gained ranging from $35,000 to < $45,000 to $55,000 to < $75,000.

6.76 The submission also provided a validation exercise comparing modelled outcomes between the 6-state and 3-state models. Overall, the base case 6-state model appeared to generate similar outcomes compared to the 3-state sensitivity analysis

but did not provide improved functionality in terms of quantifying any residual uncertainties regarding the use of subsequent therapies or validity of extrapolated long-term survival benefits.

6.77 The ESC considered the 6-state model structure introduced unnecessary complexity without improving its usefulness for decision making relative to the simplified 3-state model. The ESC noted the 3-state model produced slightly more conservative estimates of OS gain, increasing the base case ICER by approximately 10% from $45,000 to < $55,000 per QALY gained to $55,000 to < $75,000 per QALY gained (see Table 16). The ESC acknowledged the PSCR's comments that the 6-state model was chosen to explicitly include ASCT health states given the PBAC's previous advice that the absence of ASCT health states in the blinatumomab model for MRD-positive B-ALL did not adequately reflect the treatment pathways. However, the ESC considered these additional health states added substantial uncertainty as they only included on-protocol ASCT (which occurred at a similar frequency between arms).

6.78 The ESC considered that a 3-state model that incorporated a relapse-free utility estimate based on that used in the MRD-positive B-ALL submission along with OS convergence would likely be more appropriate for decision making. The ESC noted that without convergence, after 30 years, at age 80, 57.7% of patients in the blinatumomab plus standard of care arm and 33.8% of patients in the standard of care arm are alive.

6.79 The pre-PBAC response provided a revised base case that incorporated:

- the 3-state model structure
- a relapse-free utility estimate based on that used in the MRD-positive B-ALL submission (0.806) and applied to MRD-negative patients in the relapse-free disease health state
- overall survival linear convergence from 10 to 30 years
- a blinatumomab ex-manufacturer price of $| per vial.

The pre-PBAC response noted that, as per the multivariate analyses in Table 16, the revised base case resulted in an ICER of $55,000 to < $75,000 per QALY gained.

Table 16. Sensitivity analyses for the 3-state model

Analysis	Incremental cost ($)	Incremental QALY	ICER	% change
Base case	[redacted]	**3.0209**	[redacted][1]	**-**
Overall survival curve convergence (base case no convergence)				
Overall survival linear convergence from 4.5 to 30 years (base case: no convergence)	[redacted]	1.9154	[redacted][2]	+[redacted]%
Overall survival linear convergence from 10 to 30 years (base case: no convergence)		2.1906	[redacted][2]	+[redacted]%
Health state utilities (base case relapse-free 0.8534, relapsed disease 0.6920; first year post ASCT: 0.2834)				
Relapse-free 0.806 (based on MRD-positive B-ALL submission)	[redacted]	2.8641	[redacted][1]	+[redacted]%
Effective AEMP per vial (base case: $[redacted])				
Effective AEMP per vial $[redacted], based on price for MRD-positive B-ALL	[redacted]	3.0209	[redacted][3]	-[redacted]%
Multivariate analyses				
$[redacted] per vial; relapse-free utility 0.806; overall survival linear convergence from 4.5 to 30 years	[redacted]	1.8227	[redacted][2]	+[redacted]%
$[redacted] per vial; relapse-free utility 0.806; overall survival linear convergence from 10 to 30 years		2.0785	[redacted][1]	+[redacted]%

Source: The blinatumomab economic model of the submission
Abbreviations: ICER, incremental cost-effectiveness ratio; MRD, measurable residual disease; QALY, quality adjusted life year
The redacted values correspond to the following ranges
1 $55,000 to < $75,000
2 $75,000 to < $95,000
3 $45,000 to < $55,000

Drug cost/patient/course

Table 17: Drug cost per patient for blinatumomab as an add-on to consolidation chemotherapy

	Trial	Economic model	Financial estimates
Mean treatment duration	82.6 days [a]	82.6 days [a]	82.6 days [a]
Scripts per patient	-	2.95 [b]	Adult: 2.95 [b] Paediatric: 1.77 [c]
Cost per script	-	$[redacted] [d]	$[redacted] [d]
Cost/patient/course	-	$[redacted] [e]	Adult: $[redacted] [e] Paediatric: $[redacted] [e]

Source: constructed during the evaluation using the economic model and financial estimates of the submission
[a] Based on blinatumomab treatment exposure in the E1910 trial safety analysis set. The mean treatment duration was estimated based on the proportion of patients receiving each 28-day treatment cycle and mean days of treatment within each cycle
[b] Calculated based on 82.6 vials required for 82.6 treatment days and 28 vials per script
[c] Calculated based on 49.6 vials per paediatric patient (based on an assumed 0.6 adult dosing equivalent) and 28 vials per script
[d] Calculated using the proposed effective AEMP of $[redacted] per vial for 28 vials, with fees and mark-ups weighted by a 57.3%/42.7% public/private split
[e] Calculated using the estimated cost per script and scripts per patient

6.80 In the economic model, the estimated drug cost for consolidation chemotherapy per patient per course was $[redacted] (based on the E1910 consolidation protocol and assuming a mean of 87.5 treatment days across both treatment arms, using current DPMQ/DPMAs and assuming 100% public hospital use). The submission did not include costs associated with pegaspargase as it is not PBS-listed. Consolidation chemotherapy costs were not included in the financial estimates.

6.81 The estimated total drug cost for blinatumomab in combination with consolidation chemotherapy was $[redacted] in the economic model (based on 82.6 treatment days of

blinatumomab and 87.5 treatment days of consolidation chemotherapy, a total of 170.1 treatment days).

6.82 The pre-PBAC response offered a reduced blinatumomab ex-manufacturer price of $ per vial.

Estimated PBS usage & financial implications

6.83 The submission was not considered by DUSC.

6.84 The submission used an epidemiological approach to estimate the financial implications associated with the PBS listing of blinatumomab for the treatment of patients with B-ALL achieving complete haematological remission who are MRD-negative after initial induction chemotherapy. The submission used the same financial model used in the July 2019 submission for the use of blinatumomab in MRD-positive population (Blinatumomab PSD, July 2019 PBAC meeting), using the complement population and updated estimates.

6.85 Key inputs relied on in the financial estimates are summarised in Table 18 below.

Table 18: Data sources and parameter values applied in the utilisation and financial estimates

Data	Value and source	Comment
Projected number of new cases of ALL	Adult: Year 1 - [redacted][1], to Year 6 - [redacted][1]. Paediatric: Year 1 - [redacted][1] to Year 6 - [redacted][1]. Australian Cancer Incidence and Mortality (AIHW, 2017) data for 2006 to 2013 extrapolated to 2030, assuming [redacted][1] additional adult patients and [redacted][1] additional paediatric patients each year.	Updated from the July 2019 submission. Used same AIHW 2017 published data to inform the extrapolation and maintain consistency with the previous estimates. A comparison with the AIHW 2022 data showed extrapolation of 2006-2013 data underestimated cases for 2014-2021 by approximately 4.5% (138 cases). The extrapolation of estimates from the AIHW 2022 data used by the submission as a comparison with the projections using AIHW data from 2017 could not be verified and appears to be based on a different approach to the original extrapolation.
Proportion of ALL of B-cell lineage	Adult: 76% Thomas et al, 2004 (72%); Moorman et al, 2007 (assumed 78%); Oriel et al, 2010 (~71.6%); Gokbuget et al 2012 (65%); Chiaretti et al, 2013 (85.8%). Paediatric: 80% Cooper et al, 2015.	Unchanged from the July 2019 submission. The evaluator consider it was unclear why 76% was selected, given the wide range of estimates of B-cell immunophenotypes (65-85%). Some studies may have excluded mature B-cell ALL patients, which may alter the overall proportion by immunophenotype. Cooper et al. (2015) reported 80% of paediatric patients had the B-precursor immunophenotype, but the source of the estimate was not provided.
Proportion of B-ALL which is immature B-cell precursor	All: 93% Fielding et al, 2007 (approx. 2.9% mature); Moorman et al, 2010 (approx. 13.3% mature).	Unchanged from the July 2019 submission. Based on small studies with high variability. The evaluator considered it was inappropriate to apply this estimate to the paediatric population from Cooper et al. (2015), which estimated precursor B-cell ALL at 80% of paediatric ALL population.

Data	Value and source	Comment
Proportion of patients with complete remission after initial induction treatment	Adult: 88% Gokbuget et al, 2012 (90%); Holoweicki et al, 2008 (90%), Bassan et al, 2009 (84%). Paediatric: 96% Cooper 2015 (induction failure in ~3% to 5% of children with newly diagnosed ALL).	Unchanged from the July 2019 submission. The proportion of adult patients achieving complete remission decreases with advancing age, and only 68.2% of patients in the E1910 trial (aged 30-70 years) achieved CR1 after induction chemotherapy, and 58.6% maintained CR1 (ECOG performance status ≤2) after induction intensification.
Proportion of patients with complete remission MRD-negative	Adult: 60% Assumed complement of the July 2019 submission assumption of MRD-positive population (40%). Paediatric: 81% Assumed complement of the July 2019 submission assumption of MRD-positive population (19%).	Given the E1910 trial included MRD-negative (224, 78.3%) and MRD-positive (62, 21.7%) populations, the evaluator considered the assumed proportion of MRD-negative patients (60%) may be substantially underestimated. The PSCR argued that the E1910 trial is not an epidemiological study and maintained that the use of the complement of the July 2019 submission assumption remained appropriate. The July 2019 submission used a value lower than that reported in Borowitz et al. (2008), and most likely underestimated paediatric MRD positivity. The E1910 trial did not include paediatric patients.
Proportion of MRD-negative patients receiving consolidation therapy post induction	All: 95% Assumption based on clinician advice.	This is consistent with the E1910 trial, which reported 11 (3.8%) patients not commencing consolidation therapy, most frequently due to early disease progression/relapse.
Cumulative proportion of all B-ALL patients eligible for treatment	Adult: 35.453% Paediatric: 54.96% Multiplier of above proportions (product of conditional probabilities).	Same approach as the July 2019 submission. The evaluator considered the conditional multiplier used to estimate the proportion of the total B-ALL population eligible for treatment remains uncertain, given the probabilities used to derive the multipliers are unlikely to be independent.
Uptake rate	Adults: | % Paediatric: | % Assumption. The submission assumed most paediatric patients would be offered treatment in a clinical trial.	Unchanged from the July 2019 submission. Assumptions of uptake are highly uncertain. The ESC considered that uptake will be very high and considered the rates applied in the submission appropriate.
PBS units dispensed per patient per treatment course	Adult: 82.6 × 38.5 µg vials of blinatumomab over 2.95 cycles Paediatric: 49.6 × 38.5 µg vials of blinatumomab over 2.95 cycles. Assumed all patients received one 38.5 ug vial of blinatumomab daily, based on blinatumomab exposure data from the E1910 trial (2.95 scripts). [28 × 2.95 = 82.6] Paediatric patients assumed to receive 0.60 of the adult dose (1.77 scripts). [28 × (2.95 × 0.60) = 49.6]	Use of E1910 trial blinatumomab exposure by number of cycles commenced was consistent with estimates used in the economic model. The submission considered the estimate conservative, as inpatient public hospital use was included, which is not PBS subsidised. The evaluator considered this may overestimate use of blinatumomab by a maximum of 5 vials (3 vials in cycle 1 and 2 vials in cycle 2) if hospitalisation recommended in the PI is followed. The assumption that paediatric patients receive 0.60 of the adult dose was not adequately supported and is uncertain.

Data	Value and source	Comment
Cost offset for decreased blinatumomab/ inotuzumab ozogamicin use in the R/R setting	$[redacted] per patient treated with blinatumomab. Based on the incremental difference in the cost of off-protocol blinatumomab in the economic model, excluding costs of hospitalisation, bag changes and infusion pumps, accrued during the first 4.5 years of the model. The incremental costs of off-protocol blinatumomab were considered a proxy for displaced inotuzumab ozogamicin costs.	The evaluator considered the estimated cost offsets should not be considered reliable given the use of economic model outputs that were highly uncertain as the basis of these costs.

Source: Tables 4-1, 4-2 and 4-3, and Section 4.1-4.2, pp202-211 of the submission. Excel spreadsheet 'Blincyto MRD-neg B-ALL UCM section 4.xlsx' Attachment 4.1 of the submission.

Abbreviations: AIHW, Australian Institute of Health and Welfare; ALL, acute lymphoblastic leukaemia; ASCT, allogeneic haematopoietic stem cell transplant; B-ALL, B-cell precursor acute lymphoblastic leukaemia; CR, complete haematological remission; CR1, first complete haematological remission; ECOG, Eastern Cooperative Oncology Group; MRD, minimal residual disease; PBS, Pharmaceutical Benefits Scheme; R/R, relapsed/refractory

The redacted values correspond to the following ranges

1 < 500

6.86 Table 19 summarises the estimated extent of use and costs of listing blinatumomab for the treatment of patients with B-ALL achieving complete haematological remission who are MRD-negative after initial induction chemotherapy, in the first 6 years of listing.

Table 19: Estimated utilisation and cost to the PBS in the first six years of listing blinatumomab

	Year 1 (2025)	Year 2 (2026)	Year 3 (2027)	Year 4 (2028)	Year 5 (2029)	Year 6 (2030)
Estimated eligible patient population and extent of use of blinatumomab on the PBS						
Patients treated with blinatumomab - Adult (| % uptake) - Paediatric (% uptake)	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Aggregated scripts[a] - PBS - Adults - Paediatric - RPBS	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Estimated total cost of blinatumomab to the PBS/RPBS						
Total PBS/RPBS cost ($ /script)[b]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Patient copayment[c]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]
Total net PBS/RPBS cost less copayment (effective)	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Cost offsets (displaced R/R blinatumomab and inotuzumab)	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]
Total net PBS/RPBS cost less copayment	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Total cost infusion bag changes (MBS)[d]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]
Total net cost to PBS/RPBS/MBS	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]

Source: Tables 4-5, 4-6, 4-8, 4-10, 4-11, of the submission.

Abbreviations: PBS, Pharmaceutical Benefits Scheme; RPBS, Repatriation Pharmaceutical Benefits Scheme; R/R, relapsed/refractory.

[a] Assumed adults received 82.6 vials over 2.95 cycles of treatment (2.95 scripts per course of treatment), and paediatric patients received 60% of adult dose (1.77 scripts per course of treatment).

[b] Estimated weighted public/private cost per script $ based on an effective AEMP per vial of $ and 57.3% public/42.7% public use (distribution of use of blinatumomab in the R/R and MRD-positive settings (2024)).

[c] Weighted copayments PBS $19.35; RPBS $7.70, based on utilisation by beneficiary type for blinatumomab in the R/R and MRD-positive settings (2024); applied for each original script (1 for every 2 dispensings).

[d] Based on the average frequency of bag changes in the E1910 trial (one bag change every 3.0 days, equating to 9.4 bag changes per 28 days). A unit cost of $57.80 (MBS item 14221; accessing long-term implanted device for delivery of therapeutic agents) with an 80% benefit of $46.24, was applied for each bag change

The redacted values correspond to the following ranges

1 < 500

2 $10 million to < $20 million

3 net cost saving

4 $0 to < $10 million

6.87 The estimated net cost of blinatumomab to the PBS/RPBS was $10 million to < $20 million in Year 1, increasing to $10 million to < $20 million in Year 6, a total of $80 million to < $90 million over 6 years.

6.88 The estimated net cost of blinatumomab to the PBS/RBPS/MBS was $10 million to < $20 million in Year 1, increasing to $10 million to < $20 million in Year 6, a total of $80 million to < $90 million over 6 years.

6.89 The estimated eligible population was highly uncertain, given concerns with the applicability of acute lymphoblastic leukaemia incidence based on older data, as well as multiple sources used to determine the various disease- and treatment-related criteria that are unlikely to be mutually exclusive. The uptake of blinatumomab in the adult and paediatric populations was assumed, and highly uncertain. The PSCR argued that the approach to the financial estimates was the same as that accepted by the

PBAC for the complementary MRD-positive population. The PSCR noted that, as per Table 18 the parameter values were either unchanged or updated (if appropriate); or the complement of the value from the July 2019 MRD-positive submission was used. The ESC considered that uptake will be very high and considered the rates applied in the submission appropriate. The pre-PBAC response noted that the financial estimates could represent an underestimate due to the conservative assumption of a low uptake in paediatric patients.

6.90 Cost offsets associated with the reduced use of blinatumomab and inotuzumab ozogamicin in the relapsed/refractory setting based on economic model outputs are uncertain, and were considered by the evaluators as not reliable.

Quality Use of Medicines

6.91 The submission noted that the sponsor currently provides educational programs and resources for haematologists, nurses and pharmacists involved in the care of patients with B-cell precursor acute lymphoblastic leukaemia (B-ALL), and that these educational resources will be updated with a focus on the use of blinatumomab in combination with SOC chemotherapy as consolidation therapy in B-ALL.

Financial Management – Risk Sharing Arrangements

6.92 The sponsor did not propose a risk sharing arrangement (RSA), but noted that the existing Deed of Agreement, which includes an RSA for blinatumomab and inotuzumab ozogamicin in the treatment of B-ALL, reached the end of its term on 1 May 2022, and that the current expenditure cap applies to both blinatumomab and inotuzumab ozogamicin until the deed is renegotiated.

6.93 The sponsor proposed no continuing RSA for the blinatumomab and inotuzumab ozogamicin listings for the treatment of B-ALL, for the following reasons:

- The financial risk associated with blinatumomab and inotuzumab ozogamicin has not been realised over the 7 year duration of current Deed of Agreement.
- There is no risk of leakage due to the nature of the reimbursement criteria, given initial access is by written authority and access is once-in-a-lifetime under each restriction.
- Blinatumomab is judiciously used by Australian haematologists.
- The expansion of the existing restriction to allow access for MRD-negative patients, utilisation and financial impact are predictable.

6.94 The requested listing for blinatumomab is MRD-agnostic and allows for use of blinatumomab in both MRD-directed and non-MRD-directed settings. An RSA may be appropriate given uncertainties with the estimated size of the treated population and potential impact on the use of blinatumomab and inotuzumab ozogamicin as subsequent therapies.

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

7 PBAC Outcome

7.1 The PBAC deferred blinatumomab for the treatment of patients with B-cell precursor acute lymphoblastic leukaemia (B-ALL) who are measurable residual disease (MRD)-negative following induction chemotherapy. The PBAC was of a mind to recommend blinatumomab, pending advice from the Therapeutic Goods Administration Delegate. The PBAC noted that blinatumomab plus standard of care consolidation chemotherapy provided a significant improvement in overall survival and relapse-free survival over standard of care consolidation chemotherapy alone but considered the magnitude of benefit in the proposed PBS population was uncertain. The PBAC noted the revised base case and price in the pre-PBAC response and considered that based upon this the cost-effectiveness of blinatumomab was acceptable. The PBAC considered that a risk sharing arrangement (RSA) would be appropriate to address the uncertainty regarding the magnitude of benefit in the proposed PBS population and around the cost offsets associated with the reduced use of blinatumomab and inotuzumab ozogamicin in the relapsed/refractory setting.

7.2 The PBAC noted consumer comments from health care professionals, the Leukaemia Foundation and the Australian & New Zealand Childrens Haematology /Oncology Group (ANZCHOG) which highlighted the need for new frontline therapy in the treatment of B-ALL. The PBAC agreed with health care professional and ANZCHOG arguments that an age agnostic listing would be appropriate.

7.3 With regard to the requested listing and restriction, the PBAC advised that it was appropriate for:

- An Authority Required – Written listing for the initial treatment restriction and an Authority Required – Telephone/Electronic listing for the continuing treatment restriction.
- MRD-positive and MRD-negative patients to be covered in the same listing. With the inclusion of both MRD-positive and MRD-negative patients it is appropriate to include the following clinical criterion in the continuing treatment restriction 'The condition must be negative for measurable residual disease using the same method used to establish initial MRD status.'
- Inclusion of patients irrespective of Philadelphia (Ph) chromosome status or age.
- The initial treatment restriction to limit use to patients with an ECOG performance status of 0 or 1 and for a limit of 2 cycles per lifetime for each of the initial and continuing restrictions.
- Flow on changes to allow retreatment in the relapsed/refractory setting for patients who have responded to blinatumomab.

7.4 The PBAC considered standard of care chemotherapy, with or without allogeneic stem cell transplant (ASCT), was appropriate as the main comparator.

7.5 The E1910 trial provided the key evidence for blinatumomab with the PBAC noting the

risk of bias in the MRD-negative population was high given the open-label trial design. The trial used a 4-step study design to identify eligible patients with B-ALL who achieve complete haematological remission after initial induction chemotherapy and induction intensification. The PBAC noted that only 58.6% (286/488) of patients enrolled in the trial progressed to the randomised treatment phase (Step 3) where they received blinatumomab plus standard of care consolidation chemotherapy or standard of care consolidation chemotherapy alone (see paragraph 6.6). The PBAC noted that the standard of care chemotherapy regimens used in the trial were not commonly used in Australia but agreed with the ESC that this was not an issue for the applicability of the E1910 trial (see paragraph 6.18). While median overall survival was not reached in either treatment arm, the PBAC noted overall survival was statistically significantly improved in the blinatumomab plus standard of care arm compared to the standard of care arm (HR = 0.44; 95% CI: 0.25, 0.76). Similarly, the PBAC noted median relapse-free survival with also not reached in either treatment arm, but a statistically significantly improvement in relapse-free survival favouring blinatumomab was reported (HR = 0.53; 95% CI: 0.32, 0.88). The PBAC considered that the magnitude of benefit in the proposed PBS population, which is broader than the E1910 trial (e.g. in age and Ph chromosome status), was uncertain. The PBAC considered the submission claim that the treatment effects observed in the outcomes of overall survival and relapse-free survival in E1910 were independent of ASCT was uncertain but likely reasonable. In addition, the PBAC considered the long term survival benefits and magnitude of patients achieving a cure was uncertain given the relatively small numbers of patients remaining at risk beyond 4.5 years in the trial. Overall, the PBAC advised that the claim of superior comparative effectiveness was adequately supported by the clinical evidence presented.

7.6 The PBAC noted the frequency of Grade ≥3 and Grade ≥4 adverse events were similar in the blinatumomab plus standard of care arm compared to the standard of care arm of the E1910 trial. However, the incidences of neurologic events, cytokine release syndrome, and infection (sepsis, device related infections) were higher in the blinatumomab plus standard of care arm compared to the standard of care arm (see Table 11). The PBAC also noted a higher proportion of patients in the blinatumomab plus standard of care arm discontinued treatment due to adverse events (10.7%) compared to the standard of care arm (4.5%). The PBAC agreed with the ESC that the adverse event profile from E1910 was consistent with the known safety profile of blinatumomab in other indications. Overall, the PBAC considered that the submissions claim of non-inferior comparative safety was not adequately supported.

7.7 The PBAC noted the submission provided a 6-state partitioned survival model (that modelled multiple concurrent health states) as its economic model base case with a simplified 3-state model supplied as a sensitivity analysis. The PBAC agreed with the ESC that the 6-state model introduced unnecessary complexity without improving the usefulness for decision making compared to the 3-state model. While a Markov state transition model structure would be a more robust approach (see paragraph 6.52),

the PBAC agreed with the ESC that the structure of the simplified 3-state model was reliable for decision-making. The PBAC noted the 30 year time horizon was consistent with the economic evaluation of blinatumomab in the MRD-positive setting and considered this was appropriate. However, the PBAC considered the long-term survival benefits of blinatumomab in the MRD-negative setting over the 30 year time horizon were uncertain. As such, and in the context of the high risk of bias in the E1910 trial, the PBAC agreed with the ESC that it would be appropriately conservative for the overall survival curves to converge over time. In addition, the PBAC agreed with the ESC that the use of a higher utility estimate for relapse-free disease in MRD-negative patients compared to MRD-positive patients was inadequately justified. The PBAC considered that the utility estimate for relapse-free disease in MRD-positive patients (0.806) should be applied. The PBAC noted the pre-PBAC response provided a revised base case that incorporated the 3-state model structure with overall survival linear convergence from 10 to 30 years and a utility estimate of 0.806 applied to MRD-negative patients in the relapse-free disease health state. The pre-PBAC response also offered a reduced blinatumomab ex-manufacturer price of $ per vial. The PBAC considered that based upon the revised base case and price in the pre-PBAC response the cost-effectiveness of blinatumomab was acceptable.

7.8 The PBAC noted the submission used the same financial model as the July 2019 submission for the use of blinatumomab in MRD-positive population, presenting the complement population and updated estimates. The PBAC acknowledged the concerns raised by the evaluation and considered the eligible population uncertain. Specifically, the PBAC noted the proportion of adult patients with complete remission after initial induction treatment used in the financial estimate was higher than reported in the E1910 trial (88% versus 58.6%) (see Table 18). However, the PBAC noted the E1910 trial was conducted in patients aged 30-70 years and advised that the proportion of complete remission after initial induction treatment was likely higher than 58.6% in younger adults. The PBAC also noted the uptake rate for paediatric patients was assumed to be % based on the assumption that most of these patients would be offered treatment in a clinical trial. The PBAC considered this assumption uncertain and noted it may be marginally underestimated due to the recent closure of some paediatric clinical trials for this indication. The PBAC agreed with the ESC that an uptake rate of % in the adult population was appropriate. The PBAC considered that updated financial estimates should be provided with the projected number of new cases of ALL informed by AIHW 2022 data, rather than AIHW 2017 data, using the same extrapolation approach as the original extrapolation (see Table 18). The updated financial estimates should also include the revised blinatumomab price offered in the pre-PBAC response.

7.9 The PBAC noted the submission did not propose a RSA and proposed no continuing RSA for blinatumomab and inotuzumab ozogamicin for the treatment of acute lymphoblastic leukaemia. The PBAC considered that a RSA would be appropriate to address the uncertainty regarding the magnitude of benefit in the proposed PBS

population and around the cost offsets associated with the reduced use of blinatumomab and inotuzumab ozogamicin in the relapsed/refractory setting. The PBAC considered it appropriate for the existing RSA to be increased based on revised financial estimates for the total net PBS/RPBS cost.

Outcome:
Deferred

8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

9 Sponsor's Comment

Amgen is committed to working with the PBAC and Department of Health to facilitate timely access to blinatumomab for patients with MRD-negative B-ALL.

Addendum to the July 2024 PBAC public summary document:

4.01 BLINATUMOMAB, Powder for I.V. infusion 38.5 micrograms, Blincyto®, Amgen Australia Pty Limited.

10 Background

10.1 At the July 2024 meeting, the PBAC deferred blinatumomab for minimal residual disease (MRD) negative patients with B-cell precursor acute lymphoblastic leukaemia (B-ALL), but was of a mind to recommend, pending advice from the TGA Delegate.

10.2 Further, following the recent closure of a large clinical trial in the paediatric population (see paragraph 7.8), the sponsor proposed revised financial estimates and a revised risk sharing arrangement (RSA).

Registration status

10.3 The TGA Delegate's Overview became available on 30 October 2024. It was proposed that blinatumomab be registered for the following indication:

> "The treatment of B-cell precursor acute lymphoblastic leukaemia (ALL) in the consolidation phase:
>
> - In combination with chemotherapy in subjects with Philadelphia (Ph) chromosome negative disease;
> - In combination with a tyrosine kinase inhibitor in subjects with Ph chromosome positive disease, who are unable to receive chemotherapy."

The TGA Delegate stated that the evidence appeared favourable for blinatumomab as a component of consolidation therapy for adults with newly diagnosed Ph chromosome negative, MRD-negative B-ALL. The TGA Delegate noted that there were outstanding issues relating to the use in patients with Ph chromosome positive disease and for newly diagnosed and/or low risk disease in paediatric patients for which advice from the ACM was being sought.

11 Consideration of the evidence

Consumer comments

11.1 The PBAC noted the sponsor provided input from the Australian & New Zealand Children's Haematology/Oncology Group (ANZCHOG). In addition to the comments provided by ANZCHOG in July 2024 (see paragraph 6.2) the group noted the current PBS listing enabling access to two cycles of blinatumomab in the setting of measurable residual disease of precursor B-cell acute lymphoblastic leukaemia (Pre-B-cell ALL) if

certain clinical criteria are met. ANZCHOG noted that one of the clinical criteria is 'Patient must have measurable residual disease based on measurement in bone marrow, documented after an interval of at least 2 weeks from the last course of systemic chemotherapy given as intensive combination chemotherapy treatment of ALL/as subsequent salvage therapy, whichever was the later, measured using flow cytometry/molecular methods'. ANZCHOG requested the removal of the requirement for a 'two week gap between treatment and the MRD test' from all PBS blinatumomab listings. ANZCHOG stated that it is inconsistent with current treatment practices in both paediatric and adult ALL patients. The PBAC noted the requirement for a 'two week gap between treatment and the MRD test' was specified in the current measurable residual disease of Pre-B-cell ALL listings.

Estimated PBS usage & financial implications

11.2 In July 2024, the PBAC considered that new financial estimates should be provided with: (i) the projected number of new cases of ALL informed by AIHW 2022 data, rather than AIHW 2017 data, and (ii) the revised blinatumomab price offered in the July 2024 pre-PBAC response (see paragraph 7.8). At that time, the PBAC also noted that the uptake rate for paediatric patients was assumed to be [redacted]% based on the assumption that most of these patients would be offered treatment in a clinical trial. In July 2024, the PBAC considered this assumption uncertain and noted it may be marginally underestimated due to the recent closure of some paediatric clinical trials for this indication (see paragraph 7.8).

11.3 Table 20 provides a summary of the changes to financial estimates proposed by the sponsor. As more recent AIHW data had become available, data from 2024 were used (rather than 2022 data as requested).

Table 20: Summary of changes to the financial estimates

	Change	Source	Revised inputs
Updated AIHW data	Data from 2024, rather than 2017, used	Requested by PBAC in July 2024 (paragraph 7.8)	Adult patients: **July 2024** **Nov 2024** 2025: [redacted] 1 [redacted] 1 2026: [redacted] 1 [redacted] 1 2027: [redacted] 1 [redacted] 1 2028: [redacted] 1 [redacted] 1 2029: [redacted] 1 [redacted] 1 2030: [redacted] 1 [redacted] 1
Revised uptake in paediatric patients	Following the closure of the COG study AALL1731 in paediatric patients, the uptake was increased from [redacted]% to [redacted]%	In July 2024 PBAC stated that uptake in the paediatric population may be marginally underestimated due to closure of clinical trials in this population (paragraph 7.8)	Paediatric patients **July 2024** **Nov 2024** 2025: [redacted] 1 [redacted] 1 2026: [redacted] 1 [redacted] 1 2027: [redacted] 1 [redacted] 1 2028: [redacted] 1 [redacted] 1 2029: [redacted] 1 [redacted] 1 2030: [redacted] 1 [redacted] 1
Blinatumomab AEMP	Revised to equal that in the MRD-positive population	As per July 2024 pre-PBAC response	$[redacted] per vial (reduced from $[redacted])

Source: Compiled from sponsor proposal

AEMP = approved ex-manufacturer price; AIHW = Australian Institute of Health and Welfare; MRD = minimal residual disease

The redacted values correspond to the following ranges

1 < 500

11.4 Table 21 presents the revised financial estimates.

Table 21: Revised utilisation and financial estimates

	Year 1 (2025)	Year 2 (2026)	Year 3 (2027)	Year 4 (2028)	Year 5 (2029)	Year 6 (2030)
Estimated eligible patient population and extent of use of blinatumomab on the PBS						
Patients treated with blinatumomab	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1
Estimated total cost of blinatumomab to the PBS/RPBS						
Total net PBS/RPBS cost less copayment (effective)	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]2
Cost offsets (displaced R/R blinatumomab and inotuzumab)	[redacted]3	[redacted]3	[redacted]3	[redacted]3	[redacted]3	[redacted]3
Total net PBS/RPBS cost less copayment	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]2
Total cost infusion bag changes (MBS)[d]	[redacted]3	[redacted]3	[redacted]3	[redacted]3	[redacted]3	[redacted]3
Total net cost to PBS/RPBS/MBS	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]2
July 2024 PBAC meeting [a]						
Estimated eligible patient population and extent of use of blinatumomab on the PBS						
Patients treated with blinatumomab	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1
Estimated total cost of blinatumomab to the PBS/RPBS						
Total net PBS/RPBS cost less copayment (effective)	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]2
Cost offsets (displaced R/R blinatumomab and inotuzumab)	[redacted]3	[redacted]3	[redacted]3	[redacted]3	[redacted]3	[redacted]3
Total net PBS/RPBS cost less copayment	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]2
Total cost infusion bag changes (MBS)[d]	[redacted]3	[redacted]3	[redacted]3	[redacted]3	[redacted]3	[redacted]3
Total net cost to PBS/RPBS/MBS	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]2
July 2024 pre-PBAC response [b]						
Total net PBS/RPBS cost less copayment (effective)	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]2
Cost offsets (displaced R/R blinatumomab and inotuzumab)	[redacted]3	[redacted]3	[redacted]3	[redacted]3	[redacted]3	[redacted]3
Total net PBS/RPBS cost less copayment	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]2

Source: Compiled from sponsor proposal and revised post PBAC financial estimates workbook, Table 19 July 2024 PBAC minutes
R/R = relapsed and/or refractory

[a] Financial estimates presented based on the July 2024 submission EMP of $[redacted].

[b] A price reduction was offered in the July 2024 pre-PBAC response resulting in a EMP of $[redacted]. Revised financial estimates were not provided in the July 2024 pre-PBAC response and as such the only change to the July 2024 PBAC meeting estimates reported is the blinatumomab price.

The redacted values correspond to the following ranges
1 < 500
2 $10 million to < $20 million
3 $0 to < $10 million

11.5 The estimated net cost of blinatumomab to the PBS/RPBS increased from $80 million to < $90 million over the first 6 years of listing in the July 2024 submission ($70 million to < $80 million using the price offered in the July 2024 pre-PBAC response) to $80 million to < $90 million over the first 6 years of listing in the sponsors proposal.

Financial Management – Risk Sharing Arrangements

11.6 In July 2024, the PBAC considered that an RSA would be appropriate to address the uncertainty regarding the magnitude of benefit in the proposed PBS population and around the cost offsets associated with the reduced use of blinatumomab and inotuzumab ozogamicin in the relapsed/refractory setting. At that time, the PBAC considered it appropriate for the existing RSA to be increased based on revised financial estimates for the total net PBS/RPBS cost (see paragraph 7.9).

11.7 The sponsor stated that they were willing to enter into an RSA, but argued that if a [redacted]% rebate for expenditure above the caps was mandated, then the majority of the risk associated with increased use in the paediatric population would be borne by the sponsor. As such, the sponsor proposed that there could be a lower rebate for any use over the expenditure caps (e.g. [redacted]%).

12 PBAC Outcome

12.1 The PBAC recommended the Section 100 (Efficient Funding of Chemotherapy) listing of blinatumomab for the treatment of patients with B-cell precursor acute lymphoblastic leukaemia (B-ALL) who are measurable residual disease (MRD) negative following induction chemotherapy. The PBAC noted that the TGA Delegate was supportive of the registration of blinatumomab for MRD-negative B-ALL, although noted the TGA Delegate was yet to finalise the wording of the specific indication. Further, the PBAC considered that the revised financial estimates were reasonable and advised that blinatumomab should join the existing risk sharing arrangement (RSA) for blinatumomab and inotuzumab ozogamicin. As such, the PBAC was satisfied that the remaining outstanding issues relating to the application were satisfactorily resolved.

12.2 In terms of the proposed restriction, the PBAC reaffirmed its July 2024 advice that it would be appropriate if:

- The initial treatment restriction was an Authority Required – Written listing, with the continuing restriction an Authority Required – Telephone/Electronic listing.
- MRD-positive and MRD-negative patients were covered by the same listing. With the inclusion of both MRD-positive and MRD-negative patients the following clinical criterion should be included in the continuing treatment restriction 'The condition must be negative for MRD using the same method used to establish initial MRD status.'
- The restriction was agnostic with respect to both Philadelphia (Ph) chromosome status and age.
- The initial treatment restriction limited use to patients with an ECOG performance status of 0 or 1.

- Use was limited to 2 cycles per lifetime for each of the initial and continuing restrictions.
- As per the request from the Australian & New Zealand Children's Haematology/Oncology Group (ANZCHOG) outlined in paragraph 9.1, the requirement for a 'two week gap between treatment and the MRD test' be removed from the specified clinical criterion.
- A grandfathering restriction was in operation for 12 months from the initial PBS listing date.
- Flow on changes were made to allow retreatment in the relapsed/refractory setting for patients who have responded to blinatumomab.

12.3 The PBAC considered that the revised financial estimates, which incorporated 2024 AIHW data on the projected number of new ALL cases, revised the paediatric uptake from [redacted]% to [redacted]% and incorporated the blinatumomab price offered in the July 2024 pre-PBAC response, were reasonable. The PBAC considered the revised financial estimates provided an appropriate basis for an RSA.

12.4 The PBAC reaffirmed its July 2024 advice that an RSA would be appropriate to address the uncertainty regarding the magnitude of benefit in the proposed PBS population, which is broader than the E1910 trial (e.g. in age and Ph chromosome status), and around the cost offsets associated with the reduced use of blinatumomab and inotuzumab ozogamicin in the relapsed/refractory setting. The PBAC advised that blinatumomab for MRD-negative B-ALL should join the existing RSA for blinatumomab and inotuzumab ozogamicin. The PBAC advised that the expenditure caps should be adjusted to incorporate (i) the cost offsets associated with reduced use of blinatumomab and inotuzumab ozogamicin in the relapsed/refractory setting, and (ii) the increased use of blinatumomab in the MRD-negative setting. Noting that the revised RSA would account for all populations (i.e. MRD-positive and MRD-negative and relapsed/refractory disease), the PBAC considered that a rebate of [redacted]% for use above the expenditure caps would be reasonable.

12.5 The PBAC found that the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were met. Specifically, the PBAC found that in the circumstances of its recommendation for blinatumomab:

- The treatment is expected to provide a substantial and clinically relevant improvement in efficacy, over standard of care, on the basis of the results of the E1910 trial;
- The treatment is expected to address a high and urgent unmet clinical need;
- It would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A on the basis of the preceding findings.

12.6 The PBAC advised that this submission would not meet the criteria for an Independent Review as it received a positive PBAC recommendation.

Outcome:
Recommended

13 Recommended listing

13.1 Amend existing listing as follows:

Additions are in italics and deletion are in strikethrough

MEDICINAL PRODUCT Form	**PBS item code**	**Max. Amount**	**№.of Rpts**
Blinatumomab 38.5 microgram injection [1 vial] & inert substance solution [10 mL vial], 1 pack	Amend: 11850Q (Public) Amend: 11867N (Private)	784 mcg	1
Available brands			
Blincyto			
Edit Restriction Summary [new] / Treatment of Concept: [new]			
	Category / Program: Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals {Related Benefits}		
	Prescriber type: Medical Practitioners		
	Restriction type: Authority Required (in writing only via post/HPOS upload)		
	Administrative Advice: No increase in the maximum quantity or number of units may be authorised.		
	Administrative Advice: No increase in the maximum number of repeats may be authorised.		
	Administrative Advice: Special Pricing Arrangements apply.		
	Episodicity: [blank]		
	Severity: [blank]		
	Condition: [blank]		
	Indication: ~~Measurable residual disease~~ ~~of~~ Precursor B-cell acute lymphoblastic leukaemia (Pre-B-cell ALL)		
	Treatment Phase: Initial treatment ~~of measurable residual disease~~ of Pre-B-cell ALL *in complete haematological remission (CR)*		
	Treatment criteria:		
	Must be treated by a physician experienced in the treatment of haematological malignancies		
	Clinical criteria:		
	Patient must have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1		
	AND		
	Clinical criteria:		
	The condition must not be present in the central nervous system or testis		
	AND		
	Clinical criteria:		
	Patient must have achieved complete remission following intensive combination chemotherapy for initial treatment of acute lymphoblastic leukaemia (ALL) ~~or for subsequent salvage therapy~~		
	~~**AND**~~ ***OR***		
	Clinical criteria:		

	Patient must have *(i) achieved complete remission following intensive combination chemotherapy, ~~and~~ (ii)* measurable residual disease based on measurement in bone marrow, documented after ~~an interval of at least 2 weeks from~~ the last course of systemic chemotherapy given as intensive combination chemotherapy treatment of ALL/as subsequent salvage therapy, whichever was the later, measured using flow cytometry/molecular methods
	AND
	Clinical criteria:
	The treatment must not be more than 2 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.
	Prescribing Instructions: According to the TGA-approved Product Information, hospitalisation is recommended at minimum for the first 3 days of the first cycle and the first 2 days of the second cycle.
	Prescribing Instructions: For all subsequent cycle starts and re-initiation (e.g. if treatment is interrupted for four or more hours), supervision by a health care professional or hospitalisation is recommended.
	Prescribing Instructions: An amount of 784 mcg will be sufficient for a continuous infusion of blinatumomab over 28 days in each cycle.
	Prescribing Instructions: Blinatumomab is not PBS-subsidised if it is administered to an in-patient in a public hospital setting.
	Prescribing Instructions: The authority application must be made in writing and must include: (1) details of the proposed prescription; and (2) a completed ~~Measurable residual disease positive~~ Acute Lymphoblastic Leukaemia *in complete haematological remission* PBS Authority Application - Supporting Information Form; and (3) date of most recent chemotherapy, and if this was the initial chemotherapy regimen or salvage therapy; and (4) the percentage blasts in bone marrow count that is no more than 4 weeks old at the time of application.
	Prescribing Instructions: Patients who fail to demonstrate a response to PBS-subsidised treatment with this agent at the time where an assessment is required must cease PBS-subsidised therapy with this agent.
	Administrative Advice: A complete remission is defined as bone marrow blasts of less than or equal to 5%, no evidence of disease and a full recovery of peripheral blood counts with platelets of greater than 100,000 per microliter, and absolute neutrophil count (ANC) of greater than 1,000 per microliter.
	Administrative Advice: Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos Or mailed to: Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7001
Edit Restriction Summary [new] / Treatment of Concept: [new]	

		Category / Program: Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals {Related Benefits}
		Prescriber type: Medical Practitioners
		Restriction type: Authority Required (telephone/online PBS Authorities system)
		Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
		Administrative Advice: No increase in the maximum number of repeats may be authorised.
		Administrative Advice: Special Pricing Arrangements apply.
		Indication: ~~Measurable residual disease of~~ Precursor B-cell acute lymphoblastic leukaemia (Pre-B-cell ALL)
		Treatment Phase: Continuing treatment ~~of previously~~ ~~measurable residual disease~~ of Pre-B-cell ALL *in complete haematological remission (CR)*
		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
		Clinical criteria:
		Patient must have achieved a complete remission
		AND
		Clinical criteria:
		The condition must be negative for measurable residual disease (MRD) using the same method used ~~to determine initial PBS eligibility~~ *establish initial MRD status,*
		AND
		Clinical criteria:
		Patient must not have developed disease progression while receiving treatment with this drug for this condition
		AND
		Clinical criteria:
		The treatment must not be more than 2 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.
		Prescribing Instructions: For all subsequent cycle starts and re-initiation (e.g. if treatment is interrupted for four or more hours), supervision by a health care professional or hospitalisation is recommended.
		Prescribing Instructions: An amount of 784 microgram will be sufficient for a continuous infusion of blinatumomab over 28 days in each cycle.
		Prescribing Instructions: Blinatumomab is not PBS-subsidised if it is administered to an in-patient in a public hospital setting.
		Prescribing Instructions: Patients who fail to demonstrate a response to PBS-subsidised treatment with this agent at the time where an assessment is required must cease PBS-subsidised therapy with this agent.
		Administrative Advice: A complete remission is defined as bone marrow blasts of less than or equal to 5%, no evidence of disease and a full recovery of peripheral blood counts with platelets of greater than 100,000 per microliter, and absolute neutrophil count (ANC) of greater than 1,000 per microliter.

	Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).

13.2 Add new item:

MEDICINAL PRODUCT **Form**	**PBS item code**	**Max. Amount**	**№.of Rpts**
Blinatumomab 38.5 microgram injection [1 vial] & inert substance solution [10 mL vial], 1 pack	New New	784 mcg	1
Available brands			
Blincyto			
Edit Restriction Summary [new] / Treatment of Concept: [new]			
	Category / Program: Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals {Related Benefits}		
	Prescriber type: Medical Practitioners		
	Restriction type: Authority Required (in writing only via post/HPOS upload)		
	Administrative Advice: No increase in the maximum quantity or number of units may be authorised.		
	Administrative Advice: No increase in the maximum number of repeats may be authorised.		
	Administrative Advice: Special Pricing Arrangements apply.		
	Episodicity: [blank]		
	Severity: [blank]		
	Condition: [blank]		
	Indication: Precursor B-cell acute lymphoblastic leukaemia (Pre-B-cell ALL)		
	Treatment Phase: Grandfather (transition from non-PBS-subsidised treatment) of Pre-B-cell ALL in complete haematological remission (CR)		
	Treatment criteria:		
	Must be treated by a physician experienced in the treatment of haematological malignancies		
	Clinical criteria:		
	Patient must have commenced treatment with this medicine for this condition prior to [PBS listing date]		
	AND		
	Clinical criteria:		
	Patient must have had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, at initiation of non-PBS-subsidised treatment with this drug.		
	AND		
	Clinical criteria:		
	The condition must not be present in the central nervous system or testis		
	AND		
	Clinical criteria:		
	Patient must have achieved complete remission following intensive combination chemotherapy for initial treatment of acute lymphoblastic leukaemia (ALL) at initiation of non-PBS-subsidised treatment with this drug.		
	OR		
	Clinical criteria:		

	Patient must have had at initiation of non-PBS-subsidised treatment with this drug (i) achieved complete remission following intensive combination chemotherapy, (ii) measurable residual disease based on measurement in bone marrow, documented after the last course of systemic chemotherapy given as intensive combination chemotherapy treatment of ALL/as subsequent salvage therapy, whichever was the later, measured using flow cytometry/molecular methods
	AND
	Clinical criteria:
	Patient must not have developed disease progression while receiving treatment with this drug for this condition
	AND
	Clinical criteria:
	The treatment must not be more than 2 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.
	Prescribing Instructions: According to the TGA-approved Product Information, hospitalisation is recommended at minimum for the first 3 days of the first cycle and the first 2 days of the second cycle.
	Prescribing Instructions: For all subsequent cycle starts and re-initiation (e.g. if treatment is interrupted for four or more hours), supervision by a health care professional or hospitalisation is recommended.
	Prescribing Instructions: An amount of 784 mcg will be sufficient for a continuous infusion of blinatumomab over 28 days in each cycle.
	Prescribing Instructions: Blinatumomab is not PBS-subsidised if it is administered to an in-patient in a public hospital setting.
	Prescribing Instructions: The authority application must be made in writing and must include: (1) details of the proposed prescription; and (2) a completed Acute Lymphoblastic Leukaemia in complete haematological remission PBS Authority Application - Supporting Information Form; and (3) date of most recent chemotherapy, and if this was the initial chemotherapy regimen or salvage therapy; and (4) the percentage blasts in bone marrow count that is no more than 4 weeks old at the time of application.
	Prescribing Instructions: Patients who fail to demonstrate a response to PBS-subsidised treatment with this agent at the time where an assessment is required must cease PBS-subsidised therapy with this agent.
	Administrative Advice: A complete remission is defined as bone marrow blasts of less than or equal to 5%, no evidence of disease and a full recovery of peripheral blood counts with platelets of greater than 100,000 per microliter, and absolute neutrophil count (ANC) of greater than 1,000 per microliter.
	Administrative Advice: Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos Or mailed to: Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7001

	Administrative Advice: Patients may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a 'Grandfathered' patient must qualify under the 'Continuing treatment' criteria.
	Administrative Advice: This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria

13.3 Flow on changes to other PBS listed medicines for the following items 11118E (Public) and 11116C (Private) indicated for Acute lymphoblastic leukaemia (for relapsed or refractory B-cell ALL) to allow use of blinatumomab in patients who are treatment naïve as well as in patients who received blinatumomab as frontline consolidation therapy:

MEDICINAL PRODUCT Form	**PBS item code**	**Max. Amount**	**№.of Rpts**
Blinatumomab 38.5 microgram injection [1 vial] & inert substance solution [10 mL vial], 1 pack	Amend: 11118E (Public) Amend: 11116C (Private)	651 mcg	1
Available brands			
Blincyto			
Edit Restriction Summary [new] / Treatment of Concept: [new]			
	Category / Program: Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals {Related Benefits}		
	Prescriber type: Medical Practitioners		
	Restriction type: Authority Required (in writing only via post/HPOS upload)		
	Administrative Advice: No increase in the maximum quantity or number of units may be authorised.		
	Administrative Advice: No increase in the maximum number of repeats may be authorised.		
	Administrative Advice: Special Pricing Arrangements apply.		
	Episodicity: [blank]		
	Severity: [blank]		
	Condition: [blank]		
	Indication: Acute lymphoblastic leukaemia		
	Treatment Phase: Induction treatment		
	Clinical criteria:		
	The condition must be relapsed or refractory B-precursor cell ALL, with an Eastern Cooperative Oncology Group (ECOG) performance status of 2 or less		
	AND		
	Clinical criteria:		
	The condition must not be present in the central nervous system or testis		
	AND		
	Clinical criteria:		
	Patient must have previously received a tyrosine kinase inhibitor (TKI) if the condition is Philadelphia chromosome positive		
	AND		
	Clinical criteria:		
	Patient must have received intensive combination chemotherapy for initial treatment of ALL or for subsequent salvage therapy		
	AND		
	Clinical criteria:		
	Patient must not have received more than 1 line of salvage therapy		
	AND		

	Clinical criteria:
	The condition must be one of the following: (i) untreated with this drug for ~~measurable residual disease~~ *Precursor B-cell acute lymphoblastic leukaemia (Pre-B-cell ALL)*, (ii) treated with this drug for ~~measurable residual disease~~ *Pre-B-cell ALL*, but the condition has not relapsed within 6 months of completing that course of treatment
	AND
	Clinical criteria:
	The condition must have more than 5% blasts in bone marrow
	AND
	Clinical criteria:
	The treatment must not be more than 2 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.
	Prescribing Instructions: According to the TGA-approved Product Information, hospitalisation is recommended at minimum for the first 9 days of the first cycle and the first 2 days of the second cycle. For all subsequent cycle starts and re-initiation (e.g. if treatment is interrupted for 4 or more hours), supervision by a health care professional or hospitalisation is recommended.
	Prescribing Instructions: An amount of 651 microgram will be sufficient for a continuous infusion of blinatumomab over 28 days in cycle 1. An amount of 784 microgram, which may be obtained under Induction treatment - balance of supply restriction, will be sufficient for a continuous infusion of blinatumomab over 28 days in cycle 2.
	Prescribing Instructions: Blinatumomab is not PBS-subsidised if it is administered to an in-patient in a public hospital setting.
	Prescribing Instructions: The authority application must be made in writing and must include: (1) *details of the proposed prescription* ~~a completed authority prescription form~~; and (2) a completed Acute Lymphoblastic Leukaemia PBS Authority Application - Supporting Information Form; and (3) date of most recent chemotherapy, and if this was the initial chemotherapy regimen or salvage therapy, including what line of salvage; and (4) if applicable, the date of completion of blinatumomab treatment for ~~measurable residual disease~~ *Pre-B-cell ALL in CR* and the date of the patient's subsequent relapse; and (5) the percentage blasts in bone marrow count that is no more than 4 weeks old at the time of application.
	Administrative Advice: Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos Or mailed to: Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7001

These restrictions may be subject to further review. Should there be any changes made to the restriction the sponsor will be informed.

14 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

15 Sponsor's Comment

Amgen is pleased that blinatumomab will soon be available on the PBS for the treatment of minimal residual disease (MRD) negative B-cell precursor acute lymphoblastic leukaemia (B-ALL) in patients with complete haematological remission.