

5.08 EPCORITAMAB,

Solution concentrate for subcutaneous injection 4 mg in 0.8 mL,

Solution for subcutaneous injection 48 mg in 0.8 mL,
Epkinly[®],

ABBVIE PTY LTD.

1 Purpose of submission

- 1.1 The Category 1 submission requested a Section 100 (Efficient Funding of Chemotherapy Program) Authority Required (Streamlined) listing of epcoritamab, for the treatment of patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL).
- 1.2 Listing was requested on the basis of a cost-effectiveness analysis versus R-GemOx (rituximab + gemcitabine + oxaliplatin), as a proxy for rituximab-based chemoimmunotherapy treatments used in the management of relapsed or refractory DLBCL.

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

Component	Description
Population	Patients with relapsed or refractory diffuse large B-cell lymphoma after two or more lines of systemic therapy, who have also previously received or are currently unable to receive CAR-T cell therapy.
Intervention	Epcoritamab administered subcutaneously as per the recommended dosing schedule until disease progression or unacceptable toxicity.
Comparator	R-GemOx (as a proxy for rituximab-based chemoimmunotherapy treatments) administered intravenously according to the recommended dosing schedule.
Outcomes	Overall response rate, complete response rate, partial response rate, overall survival, progression-free survival, duration of response, adverse events.
Clinical claim	In patients with relapsed or refractory DLBCL after two or more lines of systemic therapy who have previously received, or are currently unable to receive CAR-T cell therapy, epcoritamab is superior in terms of efficacy, and non-inferior but different in terms of safety, compared to R-GemOx (as a proxy for rituximab-based chemoimmunotherapy treatments).

Source: Table 1-1, p3 of the submission.

Abbreviations: CAR, chimeric antigen receptor; DLBCL, diffuse large B-cell lymphoma; R-GemOx, rituximab + gemcitabine + oxaliplatin.

2 Background

Registration status

- 2.1 Epcoritamab was granted provisional TGA approval on 19 February 2024 for the following indication:
 - Treatment of adult patients with relapsed or refractory DLBCL after two or more lines of systemic therapy. Epcoritamab is not indicated for the treatment of patients with primary central nervous system lymphoma.

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- The decision to provisionally approve epcoritamab was made on the basis of overall response and duration of response results from an uncontrolled, open label phase 1/2 study (EPCORE NHL-1). Continued approval of this indication depends on verification and description of benefit in confirmatory trials.
- 2.2 The submission stated that EPCORE DLBCL-1 is the nominated confirmatory trial required for full regulatory approval. The EPCORE DLBCL-1 trial is an open-label phase 3 trial of epcoritamab versus investigator’s choice of chemoimmunotherapy (R-GemOx or bendamustine + rituximab) in approximately 480 patients with relapsed or refractory DLBCL who have failed at least one line of prior systemic therapy or are ineligible for or have already failed autologous stem cell transplantation (ASCT). The Pre-Sub-Committee Response (PSCR) stated that the EPCORE DLBCL-1 trial is an event driven study and is not anticipated to read out for at least another 12 to 18months.
- 2.3 At the time of PBAC consideration, epcoritamab was not yet registered on the ARTG. The provisional registration period for epcoritamab is two years starting on the day specified in the ARTG certificate of registration.

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

3 Requested listing

- 3.1 Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough.

MEDICINAL PRODUCT medicinal product pack	PBS item code	Dispensed Price Max Amt	Max. qty packs	Max. qty units	No. of Rpts	Available brands
EPCORITAMAB						
epcoritamab 4 mg/0.8 mL injection, 0.8 mL vial	NEW (CT)	Public hospital \$859.36 published price \$█ effective price Private hospital \$914.80 published price \$█ effective price	1	1	1	Epkinly
epcoritamab 4 mg/0.8 mL injection, 0.8 mL vial	NEW (GE)	\$█ effective price	1	1	1	Epkinly
Restrictions Summary [new1] / Treatment of Concept: [new1A]						
	Category / Program: 100 – Efficient Funding of Chemotherapy – <i>Related Benefits (Code CT) General Schedule (Code GE)</i>					
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners					
	Restriction type: <input checked="" type="checkbox"/> Authority Required (STREAMLINED)					
	Severity: Relapsed or refractory					
	Condition: Diffuse large B-cell lymphoma (DLBCL)					
	Indication: Relapsed or refractory DLBCL					
	Treatment Phase: Induction treatment					
	Clinical criteria:					
	The condition must have relapsed, or be refractory to, at least two prior systemic therapies,					
	AND					

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	Clinical criteria:
	Patient must have previously received treatment with chimeric antigen receptor-T (CAR-T) cell therapy for this condition; OR Patient must be currently unable to receive treatment with chimeric antigen receptor CAR-T cell therapy for this condition.
	AND
	Clinical criteria:
	Patient must not be eligible for stem cell transplantation.
	AND
	Clinical criteria:
	The treatment must be discontinued in patients who experience disease progression whilst on treatment.
	Prescribing Instructions:
	Prior systemic therapy may include autologous stem cell transplant.
	Prescribing Instructions:
	Grandfathered patients who have previously received non-PBS subsidised treatment with this drug for this condition prior to <LISTING DATE> must have met all the initial restriction criteria prior to initiating non-PBS subsidised treatment. A Grandfathered patient may qualify for PBS subsidised treatment under this restriction once only.
	Prescribing Instructions:
	Definition of patients unable to receive treatment with chimeric antigen receptor CAR-T cell therapy for this condition include geographical, psychosocial, clinical ineligibility or urgency.
	Administrative Advice: A dose of 0.16mg to be administered on Day 1 with initial 4mg vial. A dose of 0.8mg to be administered on Day 8 with the repeat 4mg vial. Refer to the Epcoritamab Product Information.
	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.
	Caution: Careful monitoring of patients is required due to risk of developing life-threatening Cytokine Release Syndrome (CRS).

MEDICINAL PRODUCT medicinal product pack	PBS item code	Dispensed Price Max Amt	Max. qty packs	Max. qty units	No. of Rpts	Available brands
EPCORITAMAB						
epcoritamab 48 mg/0.8 mL injection, 0.8 mL vial	NEW (CT)	Public hospital \$9,320.90 published price \$█ effective price Private hospital \$9,494.80 published price \$█ effective price	1	1	5	Epkinly
epcoritamab 48 mg/0.8 mL injection, 0.8 mL vial	NEW (GE)	\$█ effective price	1	1	5	Epkinly

Restrictions Summary [new2] / Treatment of Concept: [new2A]

	Category / Program: 100 – Efficient Funding of Chemotherapy – <i>Related Benefits (Code CT) General Schedule (Code GE)</i>
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
	Restriction type: <input checked="" type="checkbox"/> Authority Required (STREAMLINED)
	Severity: Relapsed or refractory

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Condition: Diffuse large-B-cell lymphoma (DLBCL)
Indication: Relapsed or refractory DLBCL
Treatment Phase: Continuing treatment
Clinical criteria:
Patient must have previously received PBS-subsidised treatment with this drug for this condition,
AND
Clinical criteria:
The treatment must be discontinued in patients who experience disease progression whilst on treatment.
Treatment criteria:
<i>Patient must be undergoing treatment with this drug administered weekly in cycles 1-3 – prescribe up to 9 repeats; OR</i>
<i>Patient must be undergoing treatment with this drug administered fortnightly in cycles 4-9 – prescribe up to 5 repeats; OR</i>
<i>Patient must be undergoing treatment with this drug administered every four weeks in cycles 10 and beyond – prescribe up to 2 repeats; OR</i>
Administrative Advice: Special pricing arrangements apply.
Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
Caution: Careful monitoring of patients is required due to risk of developing life-threatening Cytokine Release Syndrome (CRS).

MEDICINAL PRODUCT medicinal product pack	PBS item code	Dispensed Price Max Amt	Max. qty packs	Max. qty units	No. of Rpts	Available brands
EPCORITAMAB						
epcoritamab 48 mg/0.8 mL injection, 0.8 mL vial	NEW (CT)	Public hospital \$9,320.90 published price \$█ effective price Private hospital \$9,494.80 published price \$█ effective price	1	1	5	Epkinly
epcoritamab 48 mg/0.8 mL injection, 0.8 mL vial	NEW (GE)	\$█ effective price	1	1	5	Epkinly

Restrictions Summary [new3] / Treatment of Concept: [new3A]

Category / Program: 100 – Efficient Funding of Chemotherapy – Related Benefits (Code CT) General Schedule (Code GE)
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
Restriction type: <input checked="" type="checkbox"/> Authority Required (STREAMLINED)
Severity: Relapsed or refractory
Condition: Diffuse large B-cell lymphoma (DLBCL)
Indication: Relapsed or refractory DLBCL
Treatment Phase: Transitioning from non-PBS to PBS-subsidised treatment - Grandfathering treatment
Clinical criteria:
Patient must have received non-PBS subsidised treatment with this drug for this PBS condition prior to [PBS listing date]
AND
Clinical criteria:

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	<i>The condition must have relapsed, or be refractory to, at least two prior systemic therapies, prior to commencing treatment with this drug</i>
	AND
	Clinical criteria:
	<i>Patient must have previously received treatment with chimeric antigen receptor-T (CAR-T) cell therapy for this condition; OR Patient must have been unable to receive treatment with CAR-T cell therapy for this condition.</i>
	AND
	Clinical criteria:
	<i>Patient must not be eligible for stem cell transplantation.</i>
	AND
	Clinical criteria:
	<i>The treatment must be discontinued in patients who experience disease progression whilst on treatment.</i>
	Treatment criteria:
	<i>Patient must be undergoing treatment with this drug administered weekly in cycles 1-3 – prescribe up to 9 repeats; OR</i>
	<i>Patient must be undergoing treatment with this drug administered fortnightly in cycles 4-9 – prescribe up to 5 repeats; OR</i>
	<i>Patient must be undergoing treatment with this drug administered every four weeks in cycles 10 and beyond – prescribe up to 2 repeats; OR</i>
	Prescribing Instructions:
	<i>Prior systemic therapy may include autologous stem cell transplant.</i>
	Prescribing Instructions:
	<i>Definition of patients unable to receive treatment with CAR-T cell therapy for this condition include geographical, psychosocial, clinical ineligibility or urgency.</i>
	Administrative Advice: <i>No increase in the maximum number of repeats may be authorised.</i>
	Administrative Advice: <i>Special pricing arrangements apply.</i>
	Administrative Advice: <i>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.</i>
	Administrative Advice: <i>This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria.</i>
	Caution: <i>Careful monitoring of patients is required due to risk of developing life-threatening Cytokine Release Syndrome (CRS).</i>

- 3.2 The submission requested a special pricing arrangement with an EMP of \$ [REDACTED] per induction treatment script and \$ [REDACTED] per continuing treatment script. The pre-PBAC response offered price reduction with an EMP of \$ [REDACTED] per induction script and \$ [REDACTED] per continuing treatment script.
- 3.3 The TGA Product Information states the dosing schedule for epcoritamab includes an initial priming dose of 0.16 mg on Cycle 1 Day 1, an intermediate dose of 0.8 mg on Cycle 1 Day 8, and a full dose of 48 mg administered from Cycle 1 Day 15 and onward. The initial priming dose (0.16 mg) and the intermediate dose (0.8 mg) require dilution before subcutaneous administration, with the full doses not requiring dilution. The Efficient Funding of Chemotherapy (EFC) algorithm is not required to determine the number of vials in this case, and therefore it may be more appropriate for listing under the Section 100 EFC listing under Schedule 2 – Related Benefits where listings are

reflective of the number of vials, rather than total amount of drug. When recommending the listing of the subcutaneous form of atezolizumab in March 2024 the PBAC had considered a dual listing on the General Schedule and EFC was appropriate (paragraphs 3.2 and 6.1, atezolizumab Public Summary Document [PSD], March 2024 PBAC Meeting).

- 3.4 The submission proposed one continuing restriction with 5 repeats for all patients continuing treatment. It is noted that epcoritamab has a variable dosing within its 28-day treatment cycle depending on which treatment cycle the patient is in:
- In Cycle 1, post the initial priming dose and the intermediate dose, epcoritamab is administered weekly during the first cycle for an additional two doses;
 - From treatment Cycles 2 to 3 epcoritamab is administered weekly (four doses per cycle);
 - From treatment Cycles 4 to 9 epcoritamab is administered fortnightly (2 doses per cycle);
 - From Cycle 10 and beyond epcoritamab is administered every 28 days (one dose per cycle).

The continuing treatment phase stipulates 5 repeats which would provide 6 or 12 weeks of treatment, respectively, for patients in the weekly and fortnightly dosing phases, and 24 weeks of treatment for cycles 10 and beyond. The submission proposed to allow access to an increased number of repeats as an administrative advice in the submission; however, increasing the number of repeats would require prescribers to make such requests through Services Australia, via telephone or online therefore effectively increasing the authority level. The Secretariat proposed wording in the restriction criteria so that each prescription should be reflective of 3 months of therapy.

- 3.5 The proposed restriction is narrower than the draft TGA indication, which does not limit treatment on the basis of CAR-T cell therapy suitability or ASCT eligibility. The proposed restriction is broader than the draft TGA indication, which limits treatment to adult patients and excludes treatment of patients with primary central nervous system lymphoma.
- 3.6 The proposed restriction states that patients ‘must be currently unable to receive treatment with CAR-T cell therapy for this condition’. The definition of ‘unable to receive treatment with CAR-T cell therapy’ included in the proposed restriction is based on geographical, psychosocial, clinical ineligibility or urgency grounds. As the proposed definition is not based solely on clinical criteria, some patients who would otherwise be eligible for CAR-T cell therapy may elect treatment with epcoritamab based on a preference for a subcutaneous treatment that can be administered locally. However, CAR-T cell therapy is not nominated as a comparator in the submission. The ESC advised that this clinical criterion was subjective and may not reflect how epcoritamab would be used in clinical practice. The ESC considered the proposed

restriction would not and should not prohibit patients using CAR-T cell therapy post epcoritamab and should be removed. Clinical discretion as to the role of CAR-T vs alternative available therapies in any given line of treatment should be used. The ESC considered it may be more appropriate to strengthen the clinical criteria regarding what constitutes a line of systemic therapy for this agent. The pre-PBAC response stated that the proposed clinical criteria is not intended to prohibit patients using CAR-T cell therapy post epcoritamab. The pre-PBAC response noted that, with the recommendation by MSAC for reimbursement of CAR-T cell therapy in the second-line setting (see paragraph 4.4), CAR-T cell therapy will likely become a less relevant treatment option in third-line in the near future.

- 3.7 There may be a risk of use of epcoritamab outside of the proposed restriction as second-line treatment, particularly if the ongoing EPCORE DLBCL-1 trial demonstrates superiority of epcoritamab compared to chemoimmunotherapy. Additionally, there may be potential for use of epcoritamab in combination with other chemotherapy agents, as bridging therapy prior to CAR-T cell therapy, or as a component of salvage chemotherapy prior to ASCT. The ESC advised that it is likely that in clinical practice bispecific antibodies such as epcoritamab could be used as bridging therapy given the delay between when cells are collected for CAR-T cell therapy and when such therapy is administered. The pre-PBAC response stated that the sponsors clinical advisory board have expressed that the risk of epcoritamab being used as a bridging therapy is very low.
- 3.8 The proposed continuing treatment restriction does not include grandfathering provisions; and may require amendment to allow grandfathered treatment of patients who are already receiving the standard 48 mg dose of epcoritamab. The sponsor stated that < 500 patients initiated epcoritamab through a patient access program in 2023 and that around < 500 patients are expected to initiate epcoritamab through a patient access program in 2024.

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

4 Population and disease

- 4.1 Non-Hodgkin lymphomas (NHLs), which represent approximately 90% of lymphoma cases overall, are a heterogeneous group of lymphoproliferative disorders that develop from B lymphocytes, T lymphocytes, and occasionally natural killer cells. DLBCL is a fast-growing, aggressive form of NHL originating in B cells, and is the most common histologic subtype of large B-cell lymphoma (LBCL). DLBCL may occur *de novo* or arise from transformation of an indolent form of NHL. It is most frequently diagnosed among people over 60 years of age and affects a slightly higher proportion of males than females.
- 4.2 Patients with DLBCL commonly present with a mass reflecting enlargement of lymph nodes due to accumulation of immature and functionally deficient B lymphocytes. Symptoms vary depending on the location of affected lymph nodes and the presence

of disease in extranodal organs/tissues such as the spleen and bone marrow. General symptoms include chest, abdominal or bone pain, weight loss, fever, skin rash and fatigue. Symptoms of anaemia, extreme fatigue and an increased risk of infection and bleeding may occur as a result of bone marrow involvement.

- 4.3 While DLBCL is often curable with standard first-line chemoimmunotherapy, 30-40% of patients are either refractory to treatment or subsequently relapse. Intensive therapies, such as high dose chemotherapy followed by autologous stem cell transplantation (ASCT), CAR-T cell therapy, or chemoimmunotherapy regimens may provide long-term disease control in a proportion of patients with relapsed or refractory disease; however, some patients are not candidates for intensive treatment. In general, the approach to treatment is individualised based on patient fitness for intensive therapies, response to prior treatment, comorbid conditions, treatment availability (e.g., CAR-T cell therapy), disease factors, patient preference, and the underlying goals of treatment (long-term disease control versus palliation/symptom control).
- 4.4 The submission positioned epcoritamab as an alternative to R-GemOx and other rituximab-based chemoimmunotherapy and chemotherapy regimens, for patients who have previously received CAR-T cell therapy or are unsuitable for CAR-T cell therapy. The NCCN guidelines list CAR-T cell therapy as the preferred third or later-line therapy if not previously used, with bispecific antibody therapy (epcoritamab or glofitamab) also included as recommended treatment options in the third or later-line setting. The submission noted that CAR-T cell therapy (axicabtagene ciloleucel) received a positive recommendation for use in the second-line treatment of DLBCL at the April 2024 MSAC meeting. The submission argued that the availability of CAR-T cell therapy for use in the second-line treatment setting would not impact the use of epcoritamab, given that epcoritamab use would be restricted to the third or later-line setting. However, the ESC considered funding CAR-T cell therapy in the second-line setting may reduce the population eligible for third-line therapy as many patients will experience a long period of progression-free survival after CAR-T cell therapy.
- 4.5 Epcoritamab is a humanised IgG1-bispecific antibody that binds to CD20 on B cells and to CD3 on T cells. CD20 is expressed on most human B-cell lymphomas and leukaemias, and on B cells in peripheral blood, but not haematopoietic stem cells or plasma cells. The activity of epcoritamab is dependent upon simultaneous engagement of CD20-expressing cancer cells and CD3-expressing endogenous T cells, leading to T-cell activation and T-cell-mediated killing of CD20-expressing cells.
- 4.6 Epcoritamab is administered by subcutaneous injection. To reduce the risk of cytokine release syndrome, priming doses of 0.16 mg and 0.8 mg on Day 1 and Day 8 of Cycle 1, respectively, are given prior to the full dose of 48 mg, which is initiated on Day 15 of Cycle 1. Dosing is based on 28-day treatment cycles, with epcoritamab administered weekly during the initial 3 cycles, every 2 weeks in Cycles 4 to 9, and every 4 weeks in Cycle 10 and beyond. Treatment is ongoing until disease progression or unacceptable toxicity.

- 4.7 Premedication consisting of corticosteroids, an antihistamine and paracetamol, is recommended for all patients in Cycle 1 to reduce the risk of cytokine release syndrome. Patients who experience cytokine release syndrome may require treatment with corticosteroids and/or tocilizumab. In the EPCORE NHL-1 study, 49.6% of patients experienced cytokine release syndrome, including Grade 1 events in 30.2%, Grade 2 events in 15.8%, and Grade 3 events in 3.6% of patients. Twenty patients (29%) received treatment with tocilizumab and 14 patients (20%) received treatment with corticosteroids.

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

5 Comparator

- 5.1 The submission nominated R-GemOx, as a proxy for rituximab-based chemoimmunotherapy treatments used for the management of relapsed or refractory DLBCL, as the main comparator. The main arguments provided in support of this nomination were:

- There is no standard of care for patients with DLBCL who have received two or more lines of systemic therapy, and who are ineligible for ASCT and unable to receive CAR-T cell therapy.
- Data from the Australian Lymphoma and Related Diseases Registry (Wellard et al., 2024) suggest that R-GemOx is the most commonly used chemoimmunotherapy combination in second line relapsed/refractory DLBCL among ASCT-ineligible patients.

- 5.2 The evaluation considered chemoimmunotherapy is an appropriate comparator. However, the evaluation considered that it was unclear whether R-GemOx is a suitable proxy for the available rituximab-based chemoimmunotherapy treatments, given the large number of different regimens used, and potential differences in cost between treatment regimens. Based on an analysis of Lymphoma and Related Diseases Registry data (Wellard et al., 2024), which included 216 patients who did not receive second-line ASCT, R-DHAC (15.8%), R-GemOx (14.4%), R-ICE (rituximab + ifosfamide + carboplatin + etoposide; 11.2%) and R-CHOP 21 (rituximab + cyclophosphamide + hydroxydaunorubicin + vincristine + prednisolone; 10.7%) were the most commonly used second-line treatments out of approximately 26 different recorded treatment regimens. Among 69 patients who did not receive an ASCT as part of third-line therapy, CAR-T cell therapy (22.1%), R-GemOx (11.8%), R-ICE (8.8%) and gemcitabine + vinorelbine (7.4%) were the most commonly used third-line therapies, out of approximately 20 different treatment regimens. The ESC considered that R-GemOx is a suitable proxy for the chemoimmunotherapy options in the third-line setting. However, the ESC considered R-ICE may be used more frequently in the third-line setting if CAR-T replaces R-ICE in the second line setting. The pre-PBAC response stated that R-ICE is rarely used in third-line because patients would have received such a regimen as second-line treatment if fit enough, and would be referred to ASCT or

CAR-T at that time. The pre-PBAC response also stated that the standard protocol for R-ICE administration generally includes two in-patient hospital admission days per cycle of treatment, the cost of which has not been included in the economic model.

- 5.3 While the proposed restriction requires patients to be unable to receive CAR-T cell therapy due to reasons including geographical, psychosocial, clinical ineligibility or urgency, some patients who would otherwise be clinically suitable for CAR-T cell therapy may elect treatment with epcoritamab based on preference for a treatment that can be administered at a local treatment centre. The ESC advised that despite epcoritamab being administered by subcutaneous injection it would likely need to be prescribed by and administered with the supervision of a major treatment centre and hence it may not be more accessible for patients in rural and remote areas. The ESC agreed with the evaluation that for some patients epcoritamab may be used in preference to CAR-T cell therapy in the third-line setting (e.g. due to epcoritamab having a different adverse event profile) and that this had potential implications for its consideration as a comparator. However, the ESC noted the April 2024 positive recommendation for CAR-T cell therapy use in the second-line treatment of DLBCL and advised that public funding in this setting would make CAR-T cell therapy a less relevant comparator in the third-line setting over time.
- 5.4 The submission identified glofitamab as a near-market comparator on the basis that glofitamab has the same mechanism of action as epcoritamab (CD20/CD3 bispecific antibody), and glofitamab has provisional TGA registration for use as monotherapy for the treatment of patients with relapsed or refractory DLBCL after two or more lines of therapy. The ESC considered this was reasonable. The NCCN guidelines recommend CD20/CD3 bispecific antibodies (glofitamab or epcoritamab) as a third/subsequent line treatment for patients with relapsed/refractory disease after two prior lines of therapy. It is unclear to what extent glofitamab is currently being used in Australian clinical practice.
- 5.5 The submission noted that headline results of a phase 3 randomised controlled trial of glofitamab-GemOx versus R-GemOx, in patients with relapsed/refractory DLBCL who have received at least one prior line of therapy and are not candidates for ASCT, have recently been published (Abramson et al., 2024).

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 described how DLBCL is the commonest form of lymphoma and noted that it is often curable with standard first-line chemoimmunotherapy. However, for those who reach third-line therapy the expectation of cure is less and the clinician noted that there is no standard of care for these patients. The clinician highlighted that CAR-T cell therapy was the favoured

option in this setting but acknowledged that for complex reasons not all patients eligible for CAR-T cell therapy were accessing such therapy. The clinician considered that the availability of epcoritamab would not alter current referral patterns for CAR-T cell therapy. The clinician considered the clinical place for epcoritamab would be as proposed by the submission, in patients unable to receive CAR-T cell therapy or who have relapsed post CAR-T cell therapy. The clinician indicated that there was a clinical need for agents such as epcoritamab in this setting. In response to questions from the PBAC the clinician did not think that epcoritamab would be used as bridging therapy for CAR-T cell therapy as the period between ordering CAR-T cells and waiting for them to be delivered was short (normally between 2-3 weeks) and noted that epcoritamab has an induction period that would impact on its usefulness in this context. The clinician also noted that, while similar agents are used over a fixed duration, there are no data on how epcoritamab performs over a fixed duration rather than as ongoing treatment. As such, the clinician expected that epcoritamab would be used until disease progression in clinical practice. 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 working in regional settings described epcoritamab as an effective treatment option for patients in need that can be delivered locally. The comments noted that current treatments are available at some metropolitan hospitals, requiring patients to travel and be away from their support networks. The input from health care professionals also noted that the side effects of epcoritamab were unique, and hence requiring additional staff upskilling, but were manageable. Comments from Rare Cancers Australia highlight the difficulties faced by patients who often feel anxious about upcoming treatments and the prospect of being away from home for extended periods. The comment from Rare Cancers Australia suggested that epcoritamab offered potential benefits to patients in terms of it being a treatment that is administered subcutaneously and hence its administration is quicker and may be done in outpatient settings. Comments from Leukaemia Foundation highlighted the need for more treatment options for patients with DLBCL who have received two or more treatments as the prognosis for these patients remains poor. The comments from Leukaemia Foundation also included those from a patient who has used epcoritamab and described improvements in their quality of life with the treatment.

Clinical studies

- 6.3 No head-to-head trials comparing epcoritamab with R-GemOx were identified in the submission's literature search. Two single arm studies of epcoritamab were identified (EPCORE NHL-1 and EPCORE NHL-3).

6.4 The clinical claim was based on the following series of indirect comparisons of epcoritamab versus chemoimmunotherapy/chemotherapy:

- An unanchored matching adjusted indirect comparison (MAIC) of efficacy outcomes for epcoritamab (EPCORE NHL-1) versus chemoimmunotherapy/chemotherapy (SCHOLAR-1 pooled analysis of the MDACC, IA/MC, LY.12 and CORAL studies) in patients with no prior CAR-T cell therapy.
- An unanchored MAIC of efficacy outcomes for epcoritamab (EPCORE NHL-1) versus chemoimmunotherapy/chemotherapy (Iacoboni et al., 2024) in patients with prior CAR-T cell therapy.
- An unanchored MAIC of efficacy outcomes for epcoritamab (EPCORE NHL-1) versus chemoimmunotherapy/chemotherapy (Tomas et al., 2023) in patients with prior CAR-T cell therapy.
- A naïve comparison of safety outcomes for epcoritamab (EPCORE NHL-1) versus chemoimmunotherapy/chemotherapy (CORAL and LY.12).

6.5 The following comparisons of epcoritamab versus the near market comparator glofitamab were also presented:

- A naïve comparison of efficacy and safety outcomes for epcoritamab (EPCORE NHL-1) versus glofitamab (NP30179).
- A naïve comparison of efficacy and safety outcomes for epcoritamab (EPCORE NHL-1) versus glofitamab-GemOx (STARGLO).

6.6 Details of the studies presented in the submission are provided in Table 2.

Table 2: Studies and associated reports presented in the submission

Trial ID	Protocol title/publication title	Publication citation
Epcoritamab studies		
EPCORE NHL-1 (NCT03625037)	A Phase 1/2, Open-Label, Dose-Escalation Trial of GEN3013 in Patients with Relapsed, Progressive or Refractory B-Cell Lymphoma (EPCORE NHL-1).	Clinical study report, January 2022 data cut.
	A Phase 1/2, Open-Label, Dose-Escalation Trial of GEN3013 in Patients with Relapsed, Progressive or Refractory B-Cell Lymphoma (EPCORE NHL-1).	Clinical study report, April 2023 data cut
	Thieblemont C, Phillips T, Ghesquieres H, Cheah CY, et al. Epcoritamab, a novel, subcutaneous CD3xCD20 bispecific T-cell-engaging antibody, in relapsed or refractory large B-Cell lymphoma: dose expansion in a Phase I/II trial.	<i>J Clin Oncol</i> 2023; 41(12): 2238-2247.
	Thieblemont C, Karimi Y, Ghesquieres H, Cheah CY, et al. Extended follow-up results beyond 2.5 years from the pivotal NHL-1 EPCORE trial: subcutaneous epcoritamab monotherapy in patients with relapsed/refractory large B-cell lymphoma (R/R LBCL).	<i>J Clin Oncol</i> 2024; 42(Supp 16).
EPCORE NHL-3 (NCT04542824)	Safety and preliminary efficacy of epcoritamab (GEN3013; DuoBody – CD3Xcd20) in Japanese subjects with relapsed or refractory (R/R) B-cell non-Hodgkin lymphoma (B-NHL) - a Phase 1/2, open-label, dose-escalation trial with expansion cohorts.	Clinical study report, January 2022 data cut.

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Trial ID	Protocol title/publication title	Publication citation
	Izutsu K, Kumode T, Yuda J, Nagai H, et al. Subcutaneous epcoritamab monotherapy in Japanese adults with relapsed/refractory diffuse large B-cell lymphoma.	<i>Cancer Sci</i> 2023; 114(12): 4643-4653.
Chemoimmunotherapy/chemotherapy studies		
SCHOLAR-1	Crump M, Neelapu SS, Farooq U, Van Den Neste E, et al. Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study. Comparison of 2-year outcomes with CAR T cells (ZUMA-1) vs salvage chemotherapy in refractory large B-cell lymphoma.	<i>Blood</i> 2017; 130(16): 1800-1808. <i>Blood Adv</i> 2021; 5(20): 4149-4155.
CORAL	Van Den Neste E, Schmitz N, Mounier N, Gill D, et al. Outcome of patients with relapsed diffuse large B-cell lymphoma who fail second-line salvage regimens in the International CORAL study. Gisselbrecht C, Glass B, Mounier N, Gill DS, et al. Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era.	<i>Bone Marrow Transplant</i> 2016; 51(1): 51-57. <i>J Clin Oncol</i> 2010; 28(27): 4184-90.
LY.12	Crump M, Kuruvilla J, Couban S, MacDonald DA, et al. Randomized comparison of gemcitabine, dexamethasone, and cisplatin versus dexamethasone, cytarabine, and cisplatin chemotherapy before autologous stem-cell transplantation for relapsed and refractory aggressive lymphomas: NCIC-CTG LY.12.	<i>J Clin Oncol</i> 2024; 32(31): 3490-6.
Iacoboni et al. (2024).	Iacoboni G, Iraola-Truchuelo J, O'Reilly M, Navarro V, et al. Treatment outcomes in patients with large B-cell lymphoma after progression to chimeric antigen receptor T-cell therapy.	<i>Hemasphere</i> 2024; 8(5): e62.
Tomas et al. (2023)	Tomas AA, Fein JA, Fried S, Flynn JR, et al. Outcomes of first therapy after CD19-CAR-T treatment failure in large B-cell lymphoma.	<i>Leukemia</i> 2023; 37: 154-163.
Glofitamab studies		
NP30179 (NCT03075696)	Dickinson MJ, Carlo-Stella C, Morschhauser F, Bachy E, et al. Glofitamab for relapsed or refractory diffuse large B-cell lymphoma. Hutchings M, Morschhauser F, Iacoboni G, Carlo-Stella C, et al. Glofitamab, a novel, bivalent CD20-targeting T-cell-engaging bispecific antibody, induces durable complete remissions in relapsed or refractory B-cell lymphoma: a Phase I trial. Hutchings M, Carlo-Stella C, Morschhauser F, Falchi L, et al. Glofitamab monotherapy in relapsed or refractory large B-cell lymphoma: extended follow-up from a pivotal Phase II study and subgroup analyses in patients with prior chimeric antigen receptor T-cell therapy and by baseline total metabolic tumor volume.	<i>N Engl J Med</i> 2022; 387(24): 2220-2231. <i>J Clin Oncol</i> 2021; 39(18): 1959-1970. <i>Blood</i> 2023; 142(Supp 1): 433.
STARGLO	Abramson J, Ku M, Hertzberg M, Fox C. Glofitamab plus gemcitabine and oxaliplatin (Glofit-GemOx) for relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL): results of a global randomized phase III trial (STARGLO).	<i>European Hematology Association</i> 2024; June 2024 Annual Meeting (oral abstract and slides).

Source: Table 2-4, pp30-31; Table 2-5, pp33-34 of the submission; Table 3, p5 of Appendix A of the submission.
Selected citations relating to conference abstracts omitted.

6.7 The key features of the studies are summarised in Table 3.

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Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
Epcoritamab studies						
EPCORE NHL-1	157 ^a	Phase 1/2, open-label, single-arm, dose escalation and dose expansion study; median follow-up 25.5 months.	High	<ul style="list-style-type: none"> - Age ≥18 years with DLBCL or other aggressive B-cell non-Hodgkin lymphoma - Relapsed or refractory disease - Previously treated with ≥2 lines of systemic antineoplastic therapy - Failed prior ASCT or ineligible for ASCT - ECOG ≤2 	<ul style="list-style-type: none"> - ORR (primary) - CRR - Duration of response - Progression-free survival - Overall survival - Time to treatment discontinuation - Time to next treatment - Adverse events - HRQOL (FACT-Lym, EQ-5D-3L) 	<ul style="list-style-type: none"> - Progression-free survival - Overall survival - Time to treatment discontinuation - Time to next treatment - Adverse events - EQ-5D-3L
EPCORE NHL-3	36 ^b	Phase 1/2, open-label, single-arm, dose escalation and dose expansion study; median follow-up 8.4 months.	High	<ul style="list-style-type: none"> - Age ≥20 years and of Asian race and Japanese ethnicity - Documented mature B-cell neoplasm - Relapsed or refractory disease - Previously treated with ≥2 lines of systemic antineoplastic therapy - Not eligible for HDT with ASCT - ECOG ≤2 	<ul style="list-style-type: none"> - ORR (primary) - CRR - Duration of response - Progression-free survival - Overall survival - Time to next treatment - Adverse events 	- Not used
Chemoimmunotherapy/chemotherapy studies						
SCHOLAR-1	636 ^c	Retrospective pooled analysis of outcomes from 2 randomised studies and 2 observational cohorts; median follow- up not reported.	High	<ul style="list-style-type: none"> - Patients with refractory DLBCL who participated in the MDACC, IA/MC, LY.12 or CORAL studies - Progressive disease or stable disease after first-line R-CHOP therapy, or - relapsed following first-line treatment and had progressive disease or stable disease after second-line or later-line therapy, or - relapsed following first-line treatment, achieved a partial response or complete response to second-line/after-line therapy and experienced relapse ≤12 months after ASCT 	<ul style="list-style-type: none"> - ORR - CRR - Overall survival 	- Overall survival

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Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
Iacoboni et al. (2024)	387	Retrospective analysis of outcomes at 20 treatment centres in Spain and the UK; median follow-up 20.4 months.	High	- Patients with relapsed/refractory LBCL who experienced disease progression after third or later line treatment with CAR-T cell therapy (axicabtagene ciloleucel, tisagenlecleucel, or lisocabtagene maraleucel)	- ORR - CR - Progression-free survival - Overall survival	Not used
Tomas et al. (2023)	305	Retrospective analysis of outcomes at 2 treatment centres in the US and Israel; median follow-up 15 months.	High	- Age ≥18 years - Relapsed or refractory LBCL - Treated with CD19-directed CAR-T cell therapy (axicabtagene ciloleucel, tisagenlecleucel, lisocabtagene maraleucel, or a point-of-care CD28-based product)	- ORR - CR - Progression-free survival - Overall survival	Not used
Glofitamab studies						
NP30179	155	Phase 1/2, open-label, single-arm, dose escalation and dose expansion study; median follow-up 25.8 months.	High	- Age ≥18 years - Relapse after or failure to respond to at least one prior treatment regimen - No available treatment options that are expected to prolong survival - ECOG of 0-1	- ORR (primary) - CR - Duration of response - Progression-free survival - Overall survival - HRQOL (FACT-Lym, EORTC QLQ-C30)	Not used
STARGLO	274	Phase 3, open-label, randomised trial; median follow-up 20.7 months.	Unclear	- DLBCL (not otherwise specified) - Relapsed or refractory disease - At least one line of prior systemic therapy - Participants who have failed only one prior line of therapy must not be a candidate for ASCT - ECOG ≤2	- ORR - CRR - Duration of response - Progression-free survival - Overall survival (primary) - Adverse events - HRQOL (FACT-LymS)	Not used

Source: Section 2.4, pp45-68 of the submission; pp6-16 of Appendix A of the submission.

Abbreviations: 3L, 3-level; ASCT, autologous stem cell transplant; CAR, chimeric antigen receptor; CD, cluster of differentiation; CR, complete response; CRR, complete response rate; DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; EORTC, European Organisation for Research and Treatment of Cancer; FACT-Lym, Functional Assessment of Cancer Therapy-Lymphoma; FACT-LymS, Functional Assessment of Cancer Therapy-Lymphoma Subscale; HDT, high-dose therapy; HRQOL, health-related quality of life; ORR, overall response rate; QLQ, quality of life questionnaire; R-CHOP, rituximab + cyclophosphamide + doxorubicin + vincristine + prednisone.

^a N represents the number of patients with LBCL in the aggressive NHL dose expansion cohort.

^b N represents the number of patients with DLBCL in the monotherapy cohort of the expansion phase.

^c Includes pooled outcomes from two open-label phase 3 trials (CORAL: N=170; LY.12: N=219) and two observational cohort studies (MDACC: N=165; IA/MC: N=82).

6.8 The pivotal evidence for epcoritamab was derived from the EPCORE NHL-1 study, an ongoing, phase 1/2, open-label, single-arm study of epcoritamab monotherapy. The study included two phases: a dose escalation phase and a dose expansion phase, with

results from the dose escalation phase used to select the epcoritamab dosing regimen used in the expansion phase. The expansion phase included parallel enrolment of three cohorts of patients with aggressive NHL, indolent B-cell NHL, and mantle cell lymphoma. Results presented in the submission were for patients with DLBCL in the aggressive NHL cohort of the dose expansion phase (N=139). Clinical study reports corresponding to data cutoffs of 31 January 2022 and 21 April 2023 were provided. The PSCR provided an updated data cut of EPCORE NHL-1 (3 May 2024) with 3-years follow-up (median follow-up 37.1 months) for key efficacy endpoints.

- 6.9 Results from the EPCORE NHL-3 study, which assessed outcomes associated with epcoritamab treatment in a smaller cohort of Japanese patients, was included as supportive evidence.
- 6.10 The pivotal evidence for chemoimmunotherapy/chemotherapy treatment was derived from the SCHOLAR-1 study, a retrospective pooled analysis of four studies:
- The phase 3 LY.12 study enrolled 619 patients in 4 countries at the time of relapse after anthracycline-containing therapy. Patients were randomly assigned (first random assignment) to receive second-line GDP (gemcitabine + dexamethasone + cisplatin) or DHAP (dexamethasone + cytarabine + cisplatin) with a goal of consolidative ASCT. Eligible patients with CD20-positive lymphoma were randomly assigned to rituximab maintenance or observation after ASCT (second random assignment). Patients who participated in the study were followed up to monitor disease status and assess response to subsequent treatments.
 - The phase 3 Collaborative Trial in Relapsed Aggressive Lymphoma (CORAL) study enrolled 477 patients in 11 countries with DLBCL who were in their first relapse or whose lymphoma was refractory to first-line therapy. Patients were randomly assigned to R-ICE (rituximab + ifosfamide + etoposide + carboplatin) or R-DHAP (rituximab + dexamethasone + cytarabine + cisplatin) with a goal of consolidative ASCT (first random assignment). Eligible patients with CD20-positive lymphoma were randomly assigned to rituximab maintenance treatment or observation after ASCT (second random assignment). Patients who participated in the study were followed up to monitor disease status and assess response to subsequent treatments.
 - The MD Anderson Cancer Center (MDACC) study was a US observational cohort study of patients with DLBCL and transformed follicular lymphoma who were relapsed or refractory to initial rituximab containing chemotherapy, had failed salvage platinum-containing chemotherapy, and received a second salvage therapy at the MDACC.
 - The Molecular Epidemiology Resource of the University of Iowa/Mayo Clinic Lymphoma Specialized Program of Research Excellence (IA/MC) study was a US observational cohort study that enrolled newly diagnosed patients with lymphoma who then entered prospective documentation of primary and subsequent treatments and outcomes.

- 6.11 The SCHOLAR-1 study included patients with refractory DLBCL who participated in the CORAL, LY.12, MDACC IA/MC studies, and who met one of the following:
- Stable or progressive disease after first-line R-CHOP therapy;
 - Experienced relapse following first-line treatment and had progressive disease or stable disease after second-line or later-line therapy; or
 - Relapsed following first-line treatment, achieved a partial response or complete response to second-line/later-line therapy and experienced relapse ≤ 12 months after ASCT.
- 6.12 The ESC considered there were potential concerns about the applicability of the SCHOLAR-1 study results to the proposed PBS population. The ESC noted that patients included in the SCHOLAR-1 analysis were required to have refractory disease, and some patients had only received treatment with one prior therapy. However, the ESC advised that although there are limitations with the SCHOLAR-1 study, it can be considered representative of third-line DLBCL treatment.
- 6.13 While the submission presented the results for the SCHOLAR-1 study based on patients with evaluable data included in the original Crump et al. (2017) publication (N=523 for response outcomes; N=603 for survival outcomes), the MAIC results presented in the submission were derived using the results of an alternative analysis conducted by Neelapu et al. (2021). Neelapu et al. reported the results of a study comparing 2-year outcomes of CAR-T cell therapy (ZUMA-1) versus salvage chemotherapy (SCHOLAR-1) in patients with refractory large B-cell lymphoma. In the Neelapu et al. study, a smaller subset of patients from the SCHOLAR-1 study was included (patients with an ECOG ≥ 2 were excluded), and propensity score balancing of selected covariates was undertaken to make the ZUMA-1 and SCHOLAR-1 populations more comparable. The evaluation considered the results of the Neelapu et al. analysis should be interpreted with caution due to the included propensity score balancing, which impacted the baseline characteristics and results for patients included in the SCHOLAR-1 study. The PSCR acknowledged the limitations of the SCHOLAR-1 study data included in the Neelapu et al. (2021) publication and provided a MAIC based on data included in the original Crump et al. (2017) publication.
- 6.14 Results from two additional chemoimmunotherapy/chemotherapy studies in patients with prior CAR-T cell therapy (Iacoboni et al., 2024 and Tomas et al., 2023) were included as supportive evidence.

Comparative effectiveness

Pivotal epcoritamab study (EPCORE NHL-1)

- 6.15 Table 4 presents the results for the independent review committee-assessed response rates among patients with DLBCL in the dose expansion phase of the EPCORE NHL-1 study (April 2023 data cut). Investigator-assessed response rates (May 2024 data cut) were provided in the PSCR and are included in Table 4.

Table 4: Response results in the EPCORE NHL-1 study

Outcome	Epcoritamab IRC-assessed response (N=139, April 2023 data cut)	Epcoritamab Investigator-assessed response (N=157, May 2024 data cut)
Best overall response, n (%)		
- Complete response	56 (40.3)	64 (41)
- Partial response	30 (21.6)	NR
- Stable disease	4 (2.9)	NR
- Progressive disease	33 (23.7)	NR
- Not evaluable	16 (11.5)	NR
Overall response rate (primary outcome), n (%)	86 (61.9)	92 (59)
- 95% CI	(53.3, 70.0)	NR
Complete response rate, n (%)	56 (40.3)	64 (41)
- 95% CI	(32.1, 48.9)	NR
Partial response rate, n (%)	30 (21.6)	NR
- 95% CI	(15.1, 29.4)	NR

Source: Table 11.1, p77 of the EPCORE NHL-1 clinical study report (April 2023 data cut). Table 2, PSCR (p5).

Abbreviations: CI, confidence interval; IRC = Independent review committee.

6.16 The independent review committee-assessed overall response rate among patients treated with epcoritamab was 61.9%, including a complete response rate of 40.3% and a partial response rate of 21.6%. The best overall response was reported as not evaluable in 11.5% of patients.

6.17 Table 5 presents the results for independent review committee-assessed progression-free survival among patients with DLBCL in the dose expansion phase of the EPCORE NHL-1 study (April 2023 data cut). Investigator-assessed progression-free survival (May 2024 data cut) were provided in the PSCR and are included in Table 5. The ESC noted the updated data were investigator-assessed progression-free survival and questioned whether updated data were available for the independent review committee-assessed progression free survival. The pre-PBAC response stated that the 3-year follow-up data (May 2024 data cut) of the independent review committee-assessed outcomes were not yet available.

Table 5: Progression-free survival for the EPCORE NHL-1 study

	Epcoritamab IRC-assessed PFS (N=139 April 2023 data cut)	Epcoritamab Investigator-assessed PFS (N=157, May 2024 data cut)
Median follow-up, months (range)	22.4 (0.0-29.0)	37.1 (0.3-45.5)
Events, n (%)	94 (67.6)	NR
Median PFS, months (95% CI)	4.4 (3.0, 8.8)	4.2 (2.8, 5.5)
KM estimate of proportion remaining progression-free		
- 6 months, % (95% CI)	45.7 (37.0, 54.0)	NR
- 12 months, % (95% CI)	39.7 (31.2, 48.0)	NR
- 18 months, % (95% CI)	32.8 (24.7, 41.1)	NR
- 24 months, % (95% CI)	26.8 (18.7, 35.5)	NR

Source: Table 14.2.1.12.1, pp539-540 of the EPCORE NHL-1 clinical study report (April 2023 data cut). Table 2, PSCR (p5). EPCORE NHL-1 abstract (May 2024 data cut).

Abbreviations: CI, confidence interval; IRC = Independent review committee; KM, Kaplan-Meier; PFS, progression-free survival.

6.18 Based on a median follow-up of 22.4 months (range: 0.0-29.0), the median progression-free survival was 4.4 months (95% CI: 3.0, 8.8). The proportion of patients remaining free from progression at 24 months was 26.8% (95% CI: 18.7, 35.5). The

median progression-free survival was 27.8 months (95% CI: 23.1, not estimable) among patients achieving a complete response and 4.0 months (95% CI: 2.8, 4.4) among patients who achieved a partial response. The updated data provided in the PSCR (May 2024 data cut) indicated the median investigator-assessed progression-free survival was 37.3 months (95% CI: 26.0, not estimable) for patients who achieved a complete response and 4.2 months (95% CI: 2.8, 5.5) for all patients treated with epcoritamab.

6.19 Table 6 presents the results for overall survival among patients with DLBCL in the dose expansion phase of the EPCORE NHL-1 study.

Table 6: Overall survival results for the EPCORE NHL-1 study

	Epcoritamab (N=139, April 2023 data cut)	Epcoritamab (N=157, May 2024 data cut)
Median follow-up, months (range)	25.5 (24.4-26.1)	37.1 (0.3-45.5)
Deaths, n (%)	77 (55.4)	
Median OS, months (95% CI)	19.4 (11.7, 27.7)	18.5 (11.7, 27.7)
KM estimate of proportion remaining alive		
- 6 months, % (95% CI)	70.6 (62.2, 77.5)	NR
- 12 months, % (95% CI)	58.4 (49.6, 66.2)	NR
- 18 months, % (95% CI)	51.5 (42.7, 59.6)	NR
- 24 months, % (95% CI)	45.0 (36.3, 53.3)	NR

Source: Table 11-11, p111 of the EPCORE NHL-1 clinical study report (April 2023 data cut). Table 2, PSCR (p5).

Abbreviations: CI, confidence interval; KM, Kaplan-Meier; OS, overall survival.

6.20 Based on a median follow-up of 25.5 months, the median overall survival was 19.4 months (95% CI: 11.7, 27.7). The proportion of patients alive at 24 months was 45.0% (95% CI: 36.3, 53.3). The median overall survival was not reached (95% CI: 27.8 months, not estimable) among patients who achieved a complete response, 13.0 months (95% CI: 8.0, not estimable) among patients who achieved a partial response, and 2.9 months (95% CI: 1.8, 4.3) among non-responders.

6.21 The updated data provided in the PSCR (May 2024 data cut) indicated that at a median 37.1 months follow-up, the median overall survival was 18.5 months (95% CI: 11.7, 27.7). The median overall survival was not reached (95% CI: 36.4 months, not estimable) among patients who achieved a complete response and 63% of complete responders were alive at 36 months. The ESC considered the updated data showed that complete responses were being maintained in the context of an aggressive lymphoma.

6.22 Results were reported for a number of quality of life outcomes for patients with DLBCL in the dose expansion phase of the EPCORE NHL-1 study. Mean changes from baseline to Cycle 9 Day 1 in the EQ-5D-3L (0.094), FACT-Trial Outcome Index (8.5), FACT-G total score (4.6), FACT-Lymphoma total score (10.3), and FACT-Lymphoma Subscale (5.7) were suggestive of improvement in quality of life and/or disease symptoms. Among patients assessed at the end of treatment visit, the mean change from baseline in EQ-5D-3L indicated a small reduction in quality of life. The ESC considered quality of life outcomes were less robust than the other clinical outcomes due to the smaller number of respondents contributing data beyond Cycle 1.

Supportive epcoritamab study (EPCORE NHL-3)

6.23 Table 7 summarises the results among the 36 patients with DLBCL in the monotherapy cohort of the EPCORE NHL-3 study.

Table 7: Summary of results for the EPCORE NHL-3 study

Outcome	Epcoritamab (N=36)
Median follow-up, months (range)	8.4 (1.5-12.0)
Response rates	
Overall response rate (primary outcome), n (%) - 95% CI	20 (55.6) (38.1, 72.1)
Complete response rate, n (%) - 95% CI	16 (44.4) (27.9, 61.9)
Partial response rate, n (%) - 95% CI	4 (11.1) NR
Progression-free survival	
Median PFS, months (95% CI)	4.1 (1.2, NE)
Overall survival	
Median OS, months (95% CI) - KM estimate at 9 months	NE (8.1, NE) 59.8 (38.5, 75.8)
Duration of response	
Median duration of response, months (95% CI) - KM estimate at 9 months	NE (4.2, NE) 59.4 (28.7, 80.4)
Time to next anti-lymphoma therapy	
Median time to next anti-lymphoma therapy, months (95% CI)	5.8 (3.0, NE)

Source: Table 2-26, p78 of the submission.

Abbreviations: CI, confidence interval; KM, Kaplan-Meier; NE, not estimable; NR, not reported; OS, overall survival; PFS, progression-free survival.

6.24 At a median follow-up of 8.4 months, the overall response rate was 55.6%, median progression-free survival was 4.1 months (95% CI: 1.2, not estimable), and median overall survival was not reached (95% CI: 8.1, not estimable). The EPCORE NHL-3 study included a smaller number of patients with DLBCL than the EPCORE NHL-1 study, and the results were less mature. In general, the results appeared broadly consistent with the results for the EPCORE NHL-1 study.

Pivotal chemotherapy/chemoimmunotherapy study (SCHOLAR-1)

6.25 Table 8 presents a summary of response results for the SCHOLAR-1 study.

Table 8: Response results for the SCHOLAR-1 study

Outcome	CORAL	LY.12	MDCC	IA/MC	Pooled
Patients evaluated for response, n	170	106	165	82	523
Overall response rate, % (95% CI)	31 (NR)	26 (NR)	20 (NR)	26 (NR)	26 (21, 31)
- Complete response, % (95% CI)	15 (NR)	2 (NR)	7 (NR)	7 (NR)	7 (3, 15)
- Partial response, % (95% CI)	16 (NR)	25 (NR)	13 (NR)	18 (NR)	18 (13, 23)

Source: Table 2-27, p79 of the submission.

Abbreviations: CI, confidence interval; NR, not reported.

6.26 The reported overall response rate ranged from 20% in the MDCC cohort to 31% in the CORAL study, and was 26% for the pooled population (comprising complete responses in 7% of patients and partial responses in 18% of patients).

6.27 Table 9 presents the results for overall survival from commencement of salvage therapy for the SCHOLAR-1 study.

Table 9: Overall survival results for the SCHOLAR-1 study

Outcome	CORAL	LY.12	MDCC	IA/MC	Pooled
Patients evaluated for survival, n	170	196	165	72	603
Deaths, n	80	80	89	92	84
Median OS, months (95% CI)	6.5 (NR)	6.6 (NR)	6.6 (NR)	5.0 (NR)	6.3 (5.9, 7.0)
Proportion of surviving patients, % (95% CI)					
- 12 months	30 (NR)	31 (NR)	28 (NR)	18 (NR)	28 (25, 32)
- 24 months	22 (NR)	23 (NR)	17 (NR)	10 (NR)	20 (16, 23)

Source: Table 2-27, p79 of the submission.

Abbreviations: CI, confidence interval; NR, not reported; OS, overall survival.

6.28 The median overall survival ranged from 5.0 months in the IA/MC cohort to 6.6 months in the LY.12 study, with a pooled estimate of 6.3 months (95% CI: 5.9, 7.0). The proportion of patients remaining alive at 24 months ranged from 10% in the IA/MC cohort to 23% in the LY.12 study, with a pooled estimate of 20% (95% CI: 16, 23). Progression-free survival, time to treatment discontinuation, and time to next treatment were not reported in the SCHOLAR-1 study.

MAIC of epcoritamab (EPCORE NHL-1) versus chemoimmunotherapy (SCHOLAR-1)

6.29 The submission presented the results of an unanchored MAIC comparing efficacy outcomes for epcoritamab (EPCORE NHL-1) versus chemoimmunotherapy/chemotherapy, among patients with no prior CAR-T cell therapy (SCHOLAR-1 study). Two additional MAICs comparing efficacy outcomes for epcoritamab (EPCORE NHL-1) to chemoimmunotherapy/chemotherapy among patients who had previously received CAR-T cell therapy (Iacoboni et al., 2024; Tomas et al., 2023) were also presented in the submission.

6.30 MAICs were conducted for the outcomes of overall survival, complete response and overall response. Unanchored MAICs were conducted on the basis that the EPCORE NHL-1 study was a single-arm study without a comparator arm that could be used as a common reference.

6.31 Patient-level data for patients with DLBCL in the dose expansion cohort of the EPCORE NHL-1 study were reweighted using a propensity scoring approach to match the aggregate baseline characteristics of patients included in the SCHOLAR-1 study. Patients in EPCORE NHL-1 who had received prior CAR-T cell therapy (53/139 patients, 38.1%) were excluded from the MAIC on the basis that patients in the SCHOLAR-1 analysis had not received prior CAR-T cell therapy.

6.32 The results for the SCHOLAR-1 analysis used in the MAIC were based on the Neelapu et al. (2021) publication (N=331 for the overall survival analysis; N=340 for the response analysis), rather than the original Crump et al. (2017) publication (N=603 for overall survival comparison; N=523 for the response analysis). The evaluation considered the use of the patient characteristics and results for the SCHOLAR-1 analysis based on the Neelapu et al. analysis may not be appropriate due to the

propensity score matching applied in the Neepalu et al. study. Results incorporating patient characteristics and outcome data from the original Crump et al. (2017) publication were presented in the PSCR (see paragraph 6.40).

- 6.33 Seven variables were chosen for adjustment in the MAIC: age ≥ 65 years, male sex, ECOG score 0-1, disease stage III-IV, primary refractory disease, refractory to ≥ 2 consecutive lines of therapy, and relapse within 12 months of ASCT. The status of each of the variables as either prognostic variables, treatment effect modifier variables, or both was not specified in the technical report. The technical document stated that the adjustment weights were truncated at 1% and 99% due to outliers.
- 6.34 Table 10 presents a comparison of baseline characteristics for patients in the EPCORE NHL-1 study before and after matching for the selected variables.

Table 10: Baseline characteristics of patients in the EPCORE NHL-1 study before and after matching to the SCHOLAR-1 study

Baseline Characteristic	Unadjusted EPCORE NHL-1 (N=139)	Unadjusted EPCORE NHL-1, no prior CAR-T (N=86)	SCHOLAR-1 (N=340)	Adjusted EPCORE NHL-1, no prior CAR-T (ESS=29)
Median age, years	66.0	69.5	55.0	56.6
Age ≥ 65 years, %	52.6	61.6	16.5	18.0
Male, %	61.2	60.5	67.9	65.0
ECOG score 0-1, %	96.4	96.5	100	100
Disease stage III-IV, %	74.8	74.4	64.5	70.5
IPI score ≥ 3 , %	59.7	54.7	27.7	27.4
≥ 3 lines of therapy and/or ASCT, %	69.8	52.3	28.8	51.2
Primary refractory disease, %	58.3	45.3	37.1	40.5
Refractory to ≥ 2 consecutive therapies, %	82.0	62.8	50.0	54.6
Relapse within 12 months of ASCT, %	18.7	11.6	21.8	23.8

Source: Table 2-42, p96 of the submission.

Abbreviations: ASCT, autologous stem cell transplantation; CAR, chimeric antigen receptor; ECOG, Eastern Cooperative Oncology Group; ESS, effective sample size; IPI, International Prognostic Index.

- 6.35 After matching for the selected variables, the effective sample size was 29. There were residual differences in characteristics between the study populations, suggesting that the matching was incomplete. The submission argued that the residual differences favoured chemoimmunotherapy/chemotherapy, as a higher proportion of patients in the EPCORE NHL-1 study were treatment refractory and had received more lines of therapy after matching. The submission stated that this approach was taken as any further restriction of the adjustment would have increasingly limited the adjusted sample size and generated extreme adjustment statistical weights. Limitation of the matching of prognostic and treatment effect modifier variables in order to preserve the effective sample size may not be reasonable. Given the residual differences in the patient characteristics, it is unclear which variables were included in the MAIC-adjusted population, and to what extent they were matched.
- 6.36 Table 11 summarises the results of the unanchored MAIC for epcoritamab (EPCORE NHL-1) versus chemoimmunotherapy (SCHOLAR-1). A Kaplan-Meier plot of overall survival, before and after matching, is presented in Figure 1.

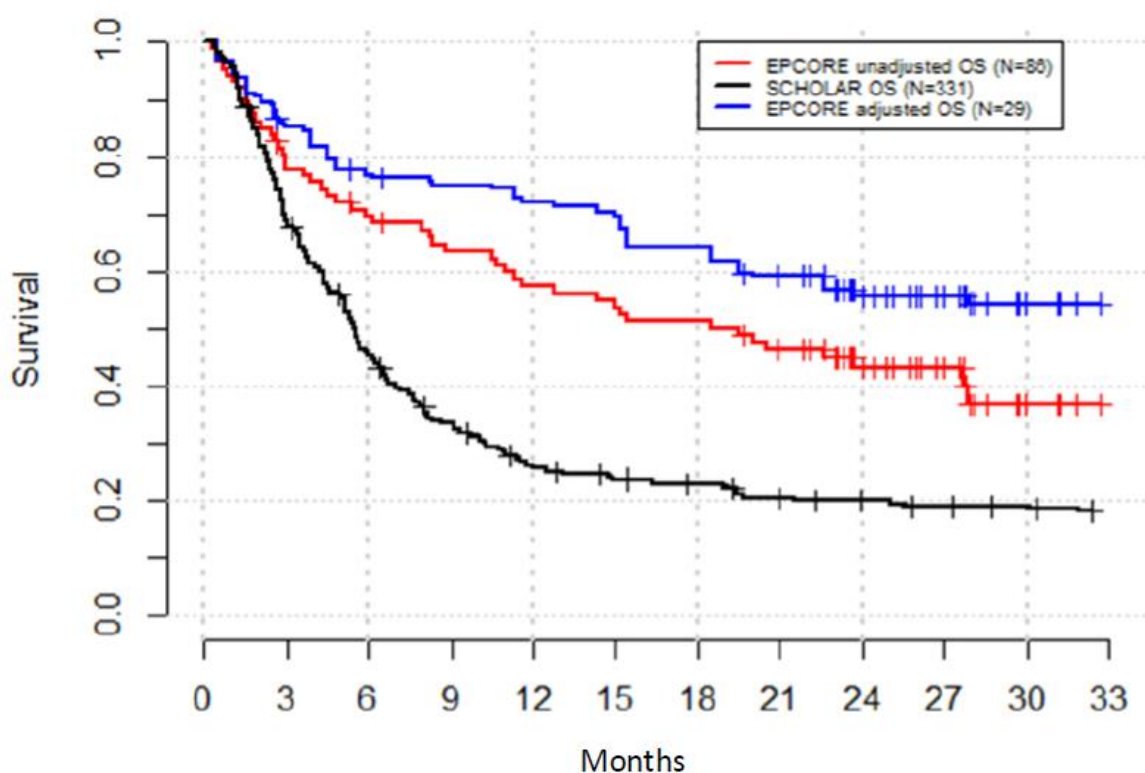
Table 11: Summary of unanchored MAIC results for epcoritamab (EPCORE NHL-1) versus chemoimmunotherapy (SCHOLAR-1)

	Unadjusted epcoritamab (N=86)	Adjusted epcoritamab (ESS =29)
Overall survival, HR (95% CI) - p-value	0.512 (0.378, 0.693) p<0.001	0.344 (0.203, 0.582) p<0.001
Complete response - Difference, % (95% CI) - p-value	Epcoritamab: 43.0% vs CIT: 12.1% 31.0% (19.9, 42.0) p<0.001	Epcoritamab: 49.5% vs CIT: 12.1% 37.4% (18.7, 56.2) p<0.001
Overall response - Difference, % (95% CI) - p-value	Epcoritamab: 67.4% vs CIT: 34.1% 33.3% (22.2, 44.5) p<0.001	Epcoritamab: 70.1% vs CIT: 34.1% 36.0% (17.9, 54.0) p<0.001

Source: Table 2-47, p102 of the submission.

Abbreviations: CI, confidence interval; ESS, effective sample size; HR, hazard ratio.

Figure 1: MAIC results for overall survival (EPCORE NHL-1 and SCHOLAR-1)



Number at risk	0	3	6	9	12	15	18	21	24	27	30	33
EPCORE NHL-1	86	66	58	52	47	44	42	36	25	17	4	0
SCHOLAR	331	227	148	108	81	73	68	59	56	52	50	0

Source: Slide 13 of the 'MAIC1_April_2023_datacut' document provided by the sponsor during the evaluation.

Abbreviations: EPCO, epcoritamab; OS, overall survival.

6.37 Prior to matching, the results for overall survival favoured epcoritamab, and the difference was nominally statistically significant (hazard ratio: 0.51; 95% CI: 0.38, 0.69). After matching, the results for overall survival favoured epcoritamab and remained nominally statistically significant (hazard ratio: 0.34; 95% CI: 0.20, 0.58). Matching was associated with a substantial improvement in survival outcomes for patients treated with epcoritamab.

- 6.38 Prior to matching, the proportion of patients achieving complete and overall responses favoured epcoritamab, and the difference was nominally statistically significant. After matching, the results favoured epcoritamab and remained nominally statistically significant.
- 6.39 The ESC agreed with the evaluation that the results of the MAIC should be interpreted with caution due to the following reasons:
- The small effective sample size after matching suggesting a lack of overlap in the EPCORE NHL-1 and SCHOLAR-1 study populations; and the impact of two patients that contributed weights of 6 and 7 to the effective sample size of 29.
 - The potential for bias due to failure to match on all relevant prognostic and treatment effect modifier variables.
 - The limited availability of patient characteristics in the Neelapu et al. (2021) publication, and the unclear impact of the propensity score matching applied to patients in the SCHOLAR-1 analysis in the Neelapu et al. study.
 - The unclear impact of the truncation on the results.
 - The limitation of patients in the SCHOLAR-1 study to refractory disease.
- 6.40 The PSCR presented the results of the SCHOLAR-1 MAIC using the Crump et al. (2017) publication. This analysis reported an adjusted overall survival (hazard ratio (HR) of 0.30 (95% CI: 0.09, 0.96) and similar (but numerically larger) incremental differences for complete response and overall response rates compared to the MAIC using the Neelapu et al. (2021) publication. The PSCR stated that the Crump et al. (2017) MAIC was not chosen for the base case as the effective sample size after adjustment was n=6. The ESC considered that the MAIC provided in the PSCR did not substantially change the clinical outcomes seen in the Neelapu et al. (2021) MAIC.
- 6.41 Overall, the ESC considered the clinical evidence presented showed that epcoritamab treatment would result in higher response rates and improved overall survival compared with chemoimmunotherapy. However, the ESC considered the results of the MAICs for overall survival and response outcomes were not sufficiently reliable to estimate incremental differences in clinical benefit.

Naïve comparison of epcoritamab (EPCORE NHL-1) and glofitamab monotherapy (NP30179)

- 6.42 Table 12 presents a naïve comparison of results for epcoritamab (EPCORE NHL-1 study) and glofitamab (NP30179 study).

Table 12: Naïve comparison of results for the EPCORE NHL-1 and NP30179 studies

Outcome	Epcoritamab (EPCORE NHL-1) (N=139)	Glofitamab (NP30179) (N=155)
Median follow-up, months (range)	25.5 (24.4-26.1)	12.6 (0.1-22.1)
Response rates (IRC-assessed)		
Overall response rate, % (95% CI)	61.9 (53.3, 70.0)	52 (43, 60)
- Complete response, % (95% CI)	40.3 (32.1, 48.9)	39 (32, 48)
- Partial response, % (95% CI)	21.6 (15.1, 29.4)	NR
Progression-free survival (IRC-assessed)		
Median PFS, months (95% CI)	4.4 (3.0, 8.8)	4.9 (3.4, 8.1)
KM estimate of duration of PFS - 12 months, % (95% CI)	39.7 (31.2, 48.0)	37 (29, 46)
Overall survival		
Median OS, months (95% CI)	19.4 (11.7, 27.7)	11.5 (7.9, 15.7)
KM estimate of duration of OS - 12 months, % (95% CI)	58.4 (49.6, 66.2)	50 (41, 58)
Duration of response (IRC-assessed)		
Median DOR, months (95% CI)	17.3 (9.7, 16.5)	18.4 (13.7, NE)
KM estimate of DOR - 12 months, % (95% CI)	58.6 (46.8, 68.6)	64 (51, 76)

Source: Table 11, p17 if Appendix A of the submission; Table 2, p2225 of Dickinson et al. (2022).

Abbreviations: CI, confidence interval; DOR, duration of response; IRC, independent review committee; NE, not estimable; OS, overall survival; PFS, progression-free survival.

6.43 Based on a naïve comparison of results, median overall survival for patients treated with glofitamab in the NP30179 study was shorter (11.5 months; 50% of patients alive at 12 months) compared to patients treated with epcoritamab in the EPCORE NHL-1 study (median overall survival 19.4 months; 58% of patients alive at 12 months). Median progression-free survival was slightly longer for glofitamab (4.9 months; 37% remaining progression-free at 12 months) compared to epcoritamab (4.4 months; 40% of patients remaining progression-free at 12 months).

Comparative harms

6.44 Table 13 presents a summary of adverse event results among patients with DLBCL in the dose expansion phase of the EPCORE NHL-1 study.

Table 13: Summary of adverse events in the EPCORE NHL-1 study

	Epcoritamab N=139	
	All AE	Treatment related AE
Median follow-up, months (range)	25.5 (0.3-32.7)	
Any AE, n (%)	138 (99.3)	117 (84.2)
Grade ≥3 AE, n (%)	96 (69.1)	47 (33.8)
Serious AE, n (%)	95 (68.3)	53 (38.1)
AE leading to treatment discontinuation, n (%)	22 (15.8)	NR
AE leading to dose delay, n (%)	55 (39.6)	NR
Fatal AE, n (%)	17 (12.2)	3 (2.2)
Grade 3 or 4 AE occurring in ≥5%, n (%)		
- Neutropenia	24 (17.3)	17 (12.2)
- Anaemia	18 (12.9)	3 (2.2)
- COVID-19	13 (9.4)	2 (1.4)
- Neutrophil count decreased	8 (5.8)	5 (3.6)
- Thrombocytopenia	7 (5.0)	2 (1.4)

Source: Table 2-30, p81; Table 2-31, pp81-82 of the submission; Table 14.3.1.11.1, pp1366-1375 of the EPCORE NHL-1 clinical study report (April 2023 data cut).

Abbreviations: AE, adverse event.

- 6.45 Grade 3 or 4 adverse events were reported for 94 (67.6%) patients, of which 45 (32.4%) were considered to be treatment related. The most commonly occurring Grade 3 or 4 adverse events (occurring in ≥5% of patients) were neutropenia (17.3%), anaemia (12.9%), COVID-19 (9.4%), neutrophil decreased (5.8%) and thrombocytopenia (5.0%). The most commonly occurring treatment-related Grade 3 or 4 adverse events (occurring in ≥2% of patients) were neutropenia (12.2%), neutrophil count decreased (3.6%), cytokine release syndrome (3.6%), anaemia (2.2%) and lymphopenia (2.2%).
- 6.46 Fatal adverse events occurred in 17 (12.2%) patients who received epcoritamab. Of these, three (one event each of immune effector cell-associated neurotoxicity syndrome (ICANS), COVID-19 pneumonia and pneumonia bacterial) were considered to be related to the study treatment.
- 6.47 Adverse events of special interest for the EPCORE NHL-1 study included cytokine release syndrome, clinical tumour lysis syndrome and ICANS. The proportion of patients experiencing at least one event of cytokine release syndrome was 49.6%, including Grade 1 events in 30.2%, Grade 2 events in 15.8%, and Grade 3 events in 3.6% of patients. Twenty patients (29%) received treatment with tocilizumab and 14 patients (20%) received treatment with corticosteroids. The mean time to onset of cytokine release syndrome was 14 days. Nine patients (6.5%) experienced at least one ICANS event. All events were Grade 1 or 2 events apart from one Grade 5 event.
- 6.48 Safety outcomes were not reported in the SCHOLAR-1 study. However, results of selected safety data were available for two of the studies included in the SCHOLAR-1 analysis (CORAL and LY.12). The submission presented a naïve comparison of safety outcomes for the EPCORE NHL-1 study and the CORAL (Gisselbrecht et al., 2010) and LY.12 (Crump et al., 2014) studies.

6.49 Table 14 presents a naïve comparison of adverse events for the EPCORE NHL-1, CORAL and LY.12 studies.

Table 14: Naïve comparison of adverse events in the EPCORE NHL-1, CORAL and LY.12 studies

	Epcoritamab	Chemoimmunotherapy/chemotherapy	
	EPCORE NHL-1 N=139	CORAL N=388	LY.12 N=610
Median follow-up, months (range)	25.5 (0.3-32.7)	27 (NR)	53 (NR)
Serious AE, n (%)	80 (57.6)	126 (32)	NR
Grade 3 or 4 AE, n (%)	94 (67.6)	NR	329 (54)
Selected Grade 3 or 4 AEs, n (%)			
- Platelet transfusion	NR	178 (46)	238 (39)
- Infection with neutropenia	NR	64 (16)	46 (8)
- Infection without neutropenia	NR	26 (7)	43 (7)
- Renal	1 (0.7)	13 (3)	NR
- Thrombosis/embolism	1 (0.7)	NR	36 (6)
- Fatigue	3 (2.2)	NR	58 (10)
- Nausea	2 (1.4)	NR	38 (6)
- Vomiting	1 (0.7)	NR	43 (7)
- Febrile neutropenia	4 (2.9)	NR	98 (16)
- Syncope	0	NR	23 (4)

Source: Table 2-50, p107 of the submission; Table A4 of the Gisselbrecht et al. (2010) supplementary appendix.

Abbreviations: AE, adverse event; NR, not reported.

6.50 The ESC considered the adverse event profiles of epcoritamab and chemoimmunotherapy appeared to be different. The ESC considered the naïve comparison had several limitations including:

- Only selected adverse events were reported in the publications for the CORAL and LY.12 studies, and there was limited overlap in the reported adverse events to allow comparisons to be made between studies.
- The results for the CORAL and LY.12 studies reflect outcomes among patients receiving second-line salvage chemotherapy with the intention to proceed to ASCT; whereas the EPCORE NHL-1 study recruited patients with ≥3 prior lines of therapy who were ineligible for ASCT.
- The included chemoimmunotherapy/chemotherapy treatments (CORAL study: R-ICE and R-DHAP; LY.12 study GDP and DHAP) did not include R-GemOx, and may not to be representative of third and subsequent-line chemoimmunotherapy treatments used for DLBCL.
- Not all patients included in the CORAL (N=388) and LY.12 studies (N=610) met the inclusion criteria for entry into the SCHOLAR-1 study.
- There were differences in patient populations and adverse event reporting periods.

Benefits/harms

6.51 On the basis of the unanchored MAIC presented in the submission, for every 100 patients treated with epcoritamab in comparison with chemoimmunotherapy over a

median duration of follow-up of 25.5 months for the EPCORE NHL-1 study (median duration of follow-up not reported for the SCHOLAR-1 study):

- Approximately 37 additional patients would achieve a complete response.
- Approximately 36 additional patients would achieve an overall response.
- Approximately 47 additional patients would remain alive at 18 months.
- Approximately 50 additional patients would experience cytokine release syndrome (a severe immune reaction causing widespread inflammation in the body).

The ESC considered the estimated benefits and harms were not reliable due to the concerns regarding the unanchored MAIC that informed these estimates (see paragraph 6.41).

Clinical claim

6.52 The submission described epcoritamab as superior in terms of effectiveness and non-inferior but different in terms of safety compared to R-GemOx (as a proxy for rituximab-based chemoimmunotherapy regimens), among patients with relapsed or refractory DLBCL, after two or more lines of systemic therapy, and who have also previously received or are currently unable to receive CAR-T cell therapy.

6.53 The ESC considered the claim of superior effectiveness was supported; however the magnitude of the clinical benefit could not be reliably estimated from the evidence presented in the submission for the following reasons:

- There was a lack of head-to-head clinical evidence to allow comparison of epcoritamab versus R-GemOx. The results of the unanchored MAICs were associated with a substantial amount of uncertainty due to the low effective sample size after matching and the limited matching of prognostic and treatment effect modifier variables, and the unclear impact of the propensity score matching applied to patients in the SCHOLAR-1 analysis in the Neelapu et al. (2021) publication. Additionally, details of the chemoimmunotherapy/chemotherapy treatments included in the SCHOLAR-1 study were not available and it is unclear whether the included treatments are representative of R-GemOx.
- The submission proposed R-GemOx to be a proxy for chemoimmunotherapy treatments used in the third and subsequent lines. However, there was limited utilisation of R-GemOx among the chemoimmunotherapy/chemotherapy treatments received by patients in the SCHOLAR-1 study, Iacoboni et al. (2024) and Tomas et al. (2023) studies.

Acknowledging that the trial is for an earlier line of therapy, the ESC considered the results of the EPCORE DLBCL-1 trial would likely be informative in addressing concerns regarding the magnitude of clinical benefit.

- 6.54 The clinical claim of non-inferior safety relied upon a naïve comparison of adverse outcomes for the EPCORE NHL-1, CORAL and LY.12 studies. However, only selected adverse events were reported in the publications for the CORAL and LY.12 studies, and there was limited overlap in the reported adverse events to allow comparison between studies. The included chemoimmunotherapy/chemotherapy treatments in the CORAL and LY.12 studies (CORAL study: R-ICE and R-DHAP; LY.12 study GDP and DHAP) did not include R-GemOx, and may not be representative of third and subsequent-line therapies, given that they were administered as second-line salvage chemotherapies among patients intending to proceed to ASCT. The ESC considered the clinical claim of non-inferior safety was not supported, and that a claim of inferior safety would be more consistent with the evidence presented in the submission. The ESC considered epcoritamab and chemoimmunotherapy have different safety profiles. The pre-PBAC response disagreed with the ESC that epcoritamab is associated with an inferior safety profile compared to chemoimmunotherapy. Instead, the pre-PBAC response argued that the risk factors and adverse effect profile of the bispecific antibody class of treatment are generally considered tolerable compared to chemoimmunotherapy.
- 6.55 A formal clinical claim versus glofitamab (nominated as a near-market comparator) was not included in the submission.
- 6.56 The PBAC considered that the claim of superior comparative effectiveness was reasonable, however, the Committee agreed with the ESC that the magnitude of the clinical benefit could not be reliably estimated from the evidence presented.
- 6.57 The PBAC agreed with the ESC that the safety profiles of epcoritamab and chemoimmunotherapy were different. The PBAC considered that claim of non-inferior comparative safety was uncertain based on the evidence presented, but may be reasonable.

Economic analysis

- 6.58 The submission presented a modelled economic evaluation comparing epcoritamab with R-GemOx (as a proxy for rituximab-based chemoimmunotherapy treatments), for the treatment of patients with relapsed or refractory DLBCL after two or more lines of systemic therapy. The economic evaluation was based on the results of the EPCORE NHL-1 and SCHOLAR-1 studies with additional modelled data. The economic evaluation was presented as a stepped cost-effectiveness/cost-utility analysis.

Table 15: Summary of model structure, key inputs and rationale

Component	Summary
Treatments	Epcoritamab versus R-GemOx (as a proxy for rituximab-based chemoimmunotherapy treatments used for the management of relapsed or refractory DLBCL).
Time horizon	20 years in the base case versus a median follow-up of 25.5 months in the EPCORE NHL-1 study.
Outcomes	Quality-adjusted life years; progression-free life years; life years.
Methods used to generate results	Partitioned survival approach during the initial 3 years; four-state Markov transition model from 3 to 20 years.
Health states	Progression-free, progressed disease, cured and dead.
Cycle length	28 days
Allocation to health states	Years 1 to 3: Partitioned survival analysis with allocation to health states based on OS and PFS curves. OS and PFS for epcoritamab based on the EPCORE NHL-1 study. OS data for R-GemOx were generated by applying the inverse of the hazard ratio derived from the unanchored MAIC of epcoritamab (EPCORE NHL-1) versus chemoimmunotherapy (SCHOLAR-1) to the overall survival data for epcoritamab. PFS for R-GemOx was derived by assuming a proportional relationship between PFS and OS for R-GemOx based on the relationship between PFS and OS for epcoritamab in the EPCORE NHL-1 study. Year 4+: Patients in the progression-free health state at 3 years move to the cured health state and are assumed to have the same life expectancy as the general population. Patients in the progressed disease state at 3 years assumed to have a median life expectancy of 6 months.
Extrapolation method	OS, PFS, TTD and TTNT Kaplan-Meier data for the epcoritamab arm extrapolated using parametric functions (OS: log-normal; PFS: log-normal; TTD: log-normal; TTNT: Gompertz). Extrapolations selected based on goodness-of-fit statistics and visual inspection. 76% of incremental QALYs and 10% of incremental costs occur in the extrapolated period.
Health related quality of life	Progression-free utility (0.730) based on the mean EQ-5D-3L utility reported at Cycle 1 Day 1 among 120 patients in the EPCORE NHL-1 study. Progressed disease utility (0.661) based on the mean EQ-5D-3L utility reported among 60 patients at the end of treatment visit in the EPCORE NHL-1 study. Cured utility (0.850) based on sponsor assumption that patients who achieve a disease cure would have a utility similar to the general Australian population.
Health state costs	Progression-free and progressed disease: \$3,048 annually based on costs reported by Goldsbury et al. (2018) in a study of long-term health care costs of Australian patients with a diagnosis of NHL (PBS costs excluded). Cured: Assumed nil cost.

Source: Table 3-1, pp116-117; Table 3-5, p130 of the submission.

Abbreviations: 3L, 3-level; DLBCL, diffuse large B-cell lymphoma; NHL, non-Hodgkin lymphoma; OS, overall survival; PFS, progression-free survival; R-GemOx, rituximab + gemcitabine + oxaliplatin; TTD, time to treatment discontinuation; TTNT, time to next treatment.

6.59 A partitioned survival approach was used to distribute patients between model health states during the initial 3 years, with the area below the progression-free survival curve corresponding to patients in the progression-free health state, the area between the progression-free and overall survival curves corresponding to patients in the progressive disease health state, and the area above the overall survival curve corresponding to patients in the dead state. From the start of Year 4, an additional health state was incorporated (cured health state), and Markov state transitions were used to distribute patients between health states.

6.60 Overall survival data for the R-GemOx arm of the model were generated by applying the inverse of the hazard ratio derived from the unanchored MAIC of epcoritamab (EPCORE NHL-1) versus chemoimmunotherapy/chemotherapy (SCHOLAR-1) to the

overall survival data for epcoritamab. The results of the MAIC were associated with substantial uncertainty and may not be a reliable measure of the relative efficacy of epcoritamab versus R-GemOx. Matching of selected variables in the MAIC was associated with a substantial improvement in survival outcomes for epcoritamab. Additionally, the applicability of the MAIC results to the proposed PBS population was unclear, as the MAIC was based on adjustment of patient characteristics in the EPCORE NHL-1 study to match the population characteristics for the SCHOLAR-1 study, which included a substantially younger population than the proposed PBS population and did not include patients with prior CAR-T cell therapy. The validity of the submission's approach of applying the inverse of the MAIC hazard ratio to the overall survival for the EPCORE NHL-1 study to derive overall survival data for the R-GemOx arm was unclear. Given the uncertainty in overall survival outcomes, the ESC considered that the use of the relatively higher unadjusted MAIC hazard ratio may provide a more conservative approach for modelling overall survival within the economic model. The pre-PBAC response noted that the Tomas et al. MAIC was provided in the main submission as supportive comparative evidence in patients who had previously failed CAR-T cell therapy, and was included in the sensitivity analysis of the economic model (see Table 18). The pre-PBAC response proposed that the hazard ratio of 0.44 reported in the Tomas et al MAIC be used. The PBAC considered the results of the Tomas et al MAIC were highly uncertain due to the small effective sample sizes after matching, the unclear impact of the 1% and 99% truncation used, and the residual differences between trials and trial populations.

- 6.61 Progression-free survival was not reported for the SCHOLAR-1 study. In the absence of progression-free survival data for the R-GemOx arm, a proportional approach was used to estimate progression-free survival. Overall survival for R-GemOx (derived by applying the inverse of the MAIC hazard ratio to the EPCORE NHL-1 overall survival results) was multiplied by the epcoritamab progression-free survival divided by the epcoritamab overall survival. The method used to derive progression-free survival was not adequately justified and it is unclear whether the derived progression-free survival reflects the progression-free survival associated with chemoimmunotherapy/R-GemOx. In the absence of progression-free survival data for the SCHOLAR-1 study, the evaluation considered it would have been preferable to obtain progression-free survival data from an alternative source. The ESC noted that the current model was not overly sensitive to progression-free survival.
- 6.62 All patients were assumed to cease treatment with epcoritamab at 3 years, based on the assumption that patients in the progression-free health state at 3 years are cured (and patients in the progressed-disease state discontinue treatment with epcoritamab at the time of disease progression). The ESC noted that the PSCR stated that updated data from EPCORE NHL-1 (median follow-up 37.1 months for the May data cut) demonstrated that 12% of patients remained on treatment at 3 years. The ESC considered the ongoing use of epcoritamab should be captured in the economic model. The pre-PBAC response noted the concern raised by the ESC that patients and

clinicians may be reluctant to discontinue treatment at 3 years if a durable and remission has been achieved. However, the pre-PBAC response argued against the use of epcoritamab being captured in the model beyond the re-specified cure timing of 5 years, stating that clinician input indicates any such reluctance to discontinue epcoritamab will have been eliminated after 5 years of treatment.

6.63 The ESC agreed with the evaluation that there is a lack of evidence to support the assumption of a cure at 3 years among patients receiving treatment of relapsed or refractory DLBCL in the third or subsequent treatment line. The ESC noted that MSAC had accepted a mixture cure model for the CAR-T cell therapy axicabtagene ciloleucel for second line DLBCL that assumed a proportion of patients were ‘cured’ if they were event-free after 5 years (axicabtagene ciloleucel MSAC PSD; April 2024). The ESC noted the approach accepted by MSAC was considered clinically plausible and consistent with longer term evidence of a plateau in overall survival curves. The ESC considered an assumption of cure for progression-free patients at 5 years may be reasonable in the current submission. The pre-PBAC response accepted a 5-year cure assumption.

6.64 Table 16 summarises the key drivers of the economic model.

Table 16: Key drivers of the model

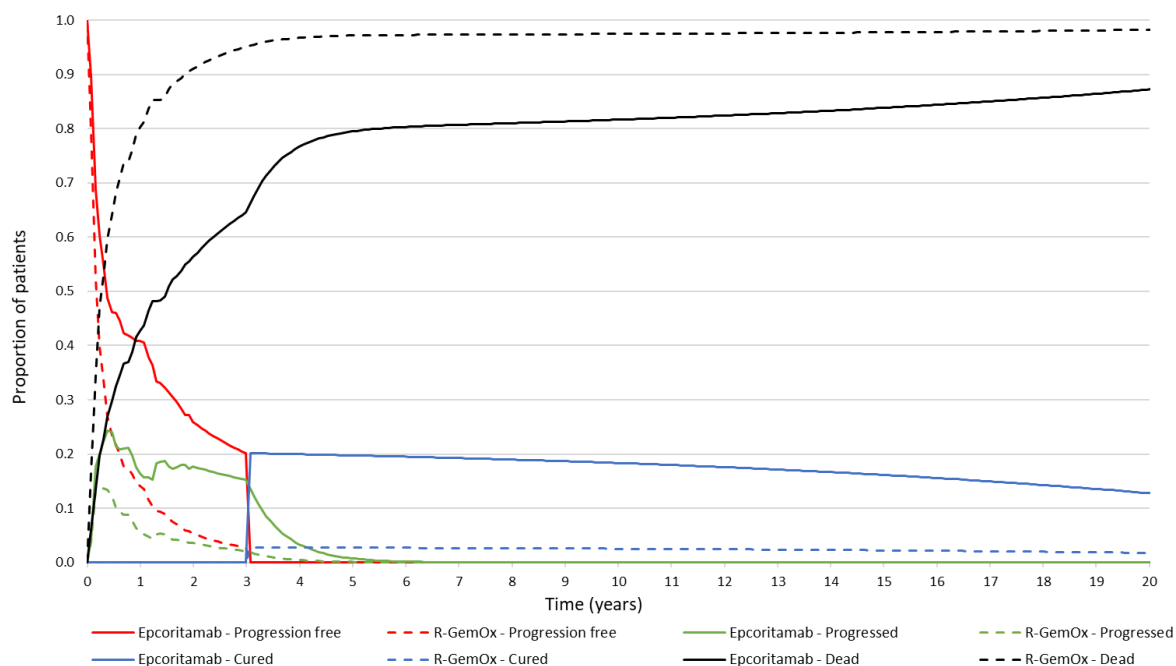
Description	Method/Value	Impact
Cure assumption	All patients in the progression-free health state at 3 years are assumed to be cured of DLBCL and enter the cured health state. Patients in the cured state are assumed to experience a similar mortality risk to the general population based on Australian life tables. All patients entering the cured health state were assumed to discontinue epcoritamab treatment. The ESC agreed with the evaluation that the assumption of a cure for all patients remaining progression-free at 3 years was considered highly uncertain, as there is currently a lack of data to inform long term outcomes associated with epcoritamab treatment. Based on a median follow-up of 25.5 months in the EPCORE NHL-1 study, there was no indication of plateauing of overall survival. Additionally, the proposed population includes patients with relapsed or refractory disease receiving third or later-line treatment and it is unclear if patients remaining progression-free whilst on active treatment with epcoritamab will be cured. The ESC considered an assumption of cure for progression-free patients at 5 years may be reasonable for this submission (see paragraph 6.63). The pre-PBAC response accepted a 5-year cure assumption.	High, favours epcoritamab
R-GemOx overall survival	Derived by applying the inverse of the hazard ratio obtained from the unanchored MAIC of epcoritamab (EPCORE NHL-1) versus chemoimmunotherapy/chemotherapy (SCHOLAR-1) to the overall survival results for the epcoritamab arm. The results of the MAIC were considered highly uncertain due to the small effective sample size after matching, the potential impact of two patients that contributed weights of 6 and 7 patients to the effective sample size out the effective sample size of 29, the limited availability of patient characteristics in the Neelapu et al. (2021) publication, the potential for bias due to failure to match on all relevant prognostic and treatment effect modifier variables, and the limitation of patients in the SCHOLAR-1 study to refractory disease.	High, favours epcoritamab
Time horizon	20 years in the base case. The modelled results over the 20-year time horizon were associated with a large degree of uncertainty due to the absence of comparative overall survival and progression-free survival data for epcoritamab versus R-GemOx, and the assumption that all patients remaining progression-free at 3 years could be considered cured of DLBCL. The ESC considered a reduced time horizon would be more appropriate.	Moderate, favours epcoritamab

Source: Constructed during the evaluation.

Abbreviations: DLBCL, diffuse large B-cell lymphoma; R-GemOx, rituximab + gemcitabine + oxaliplatin.

6.65 Figure 2 presents model traces for the epcoritamab and R-GemOx arms.

Figure 2: Model traces for the epcoritamab and R-GemOx arms of the economic model



Source: 'Results' tab of the Section 3 economic model Excel workbook.
Abbreviations: R-GemOx, rituximab + gemcitabine + oxaliplatin.

6.66 Approximately 20% of patients in the epcoritamab arm remain progression-free at 3 years and enter the cured health state compared to 3% of patients in the R-GemOx arm. At 3 years, approximately 14% of patients in the epcoritamab arm are in the progressed disease state compared to 2% in the R-GemOx arm; and approximately 65% of patients in the epcoritamab and 95% of patients in the R-GemOx arm are dead. Among patients entering the cure state at 3 years, 63% remain alive at 20 years. The proportions of patients in the epcoritamab arm remaining free from progression at 2 years and remaining alive at 2 years were consistent with the reported EPCORE NHL-1 study results (27% and 45%, respectively).

6.67 Data provided by the Australian Lymphoma and Related Diseases Registry (Wellard et al., 2024) on progression-free survival from the commencement of third-line therapy indicated that approximately 15% of patients remain progression-free at 1 year and 12.5% at 2 years; with overall survival from the commencement of third-line therapy of 37.5% at 1 year and 25% at 2 years. This was generally higher than the modelled progression-free survival (14% and 5% at 1 year and 2 years, respectively) and overall survival (20% and 9% at 1 year and 2 years, respectively) among patients in the R-GemOx arm, noting that few patients remain at risk at 2 years in the Wellard et al. data. Additionally, median overall survival among patients in the R-GemOx arm of the STARGLO trial (which included patients with relapsed or refractory DLBCL with at least 1 prior therapy versus at least 2 prior therapies in the EPCORE NHL-1 study) was substantially longer (12.9 months) than the modelled overall survival for the R-GemOx

arm (3 months). The PSCR argued that the Australian Lymphoma and Related Diseases Registry survival data may not be representative of the survival among patients treated with chemoimmunotherapy, as the registry sample included a large proportion of patients who received treatment with CAR-T cell therapy (14%; 15/106) or participated in a clinical trial (31%; 33/106) as their third-line intervention. The PSCR also argued that the comparison with the STARGLO trial was not appropriate given that most patients had received only 1 prior line of therapy. The ESC considered there was a lack of alternative data to validate the modelled survival outcomes for the chemoimmunotherapy/R-GemOx arm in the economic model. The ESC noted the progression-free survival and overall survival estimates from the EPCORE NHL-1 May 2024 data cut provided in the PSCR were slightly more conservative than the April 2023 data cut. The ESC considered that updating the economic model with the data provided in the PSCR may assist in validating the modelling for overall survival. The pre-PBAC response noted that the progression-free survival and overall survival estimates from the EPCORE NHL-1 May 2024 data cut were overlain with the same curves from the April 2023 data cut and argued that the similarity in the data indicated the model did not require updating for the later data cut.

- 6.68 The ESC noted the starting age in the economic model (63.7 years based on the ECPORE NHL-1 trial) was lower than the reported median age of patients initiating third-line therapy in the Australian Lymphoma and Related Diseases Registry (66.8 years)(Wellard et al., 2024). The ESC considered that given the age of patients and the severity of the condition a 20 year time horizon was not appropriate. Based on the age of the proposed population, combined with the concerns raised regarding the uncertainty in the modelling of overall survival, the ESC advised a 10-year time horizon may be more appropriate. The pre-PBAC response argued that in the context of a longer time to be considered cured (i.e. 5 years), the revised base case should maintain a 20-year time horizon.
- 6.69 Table 17 presents the results of the stepped economic evaluation. During the evaluation, errors associated with the health state costs (annual cost of \$3,048 included in each cycle rather than 28-day cost of \$233.68) and double-counting of the adverse event costs were corrected.

Table 17: Results of the stepped economic evaluation

Step and component	Epcoritamab	R-GemOx	Increment
Step 1: Trial-based analysis over 25.5 months based on a naïve comparison of results for the EPCORE NHL-1 and SCHOLAR-1 studies; including drug, administration and adverse event costs.			
Costs	\$█	\$4,273	\$█
Overall response	61.9%	26.0%	35.9%
Patients alive at 2 years	42%	20%	22%
Incremental cost/overall response gained			\$ ¹
Incremental cost/additional patient alive at 2 years			\$ ²
Step 2: Modelled analysis over 25.5 months with application of the MAIC hazard ratio to derive OS for the R-GemOx arm; PFS and TTD for R-GemOx arm estimated by assuming a proportional relationship between PFS and OS for PFS, and TTD and PFS for TTD.			
Costs	\$█	\$4,273	\$█
Progression-free life years gained	0.850	0.404	0.447
Life years gained	1.210	0.542	0.668
Incremental cost/life year gained			\$ ³
Incremental cost/progression-free life year gained			\$ ¹
Step 3: Incorporation of health state utilities and adverse event disutilities.			
Costs	\$█	\$4,273	\$█
QALYs gained	0.856	0.384	0.473
Incremental cost/QALY gained			\$ ³
Step 4: Time horizon increased to 20 years.			
Costs	\$█	\$4,273	\$█
Life years gained	3.291	0.690	2.601
QALYs gained	2.307	0.488	1.819
Incremental cost/LY gained			\$ ⁴
Incremental cost/QALY gained			\$ ⁵
Step 5: Inclusion of health state costs.			
Costs	\$█	\$6,377	\$█
QALYs gained	2.307	0.488	1.819
Incremental cost/QALY gained			\$ ⁵
Step 6: Inclusion of cure assumption at 3 years.			
Costs	\$█	\$6,115	\$█
QALYs gained	2.635	0.635	2.000
Incremental cost/QALY gained (base case)			\$ ⁴

Source: Constructed using the Section 3 economic model Excel workbook; Table 3-30, p165 of the submission.

Abbreviations: MAIC, matching adjusted indirect comparison; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life year; R-GemOx, rituximab + gemcitabine + oxaliplatin.

Note: Errors associated with the health state costs (annual cost of \$3,048 included in each cycle rather than 28-day cost of \$233.68) and double-counting of the adverse event costs were corrected during the evaluation.

The redacted values correspond to the following ranges:

¹ \$255,000 to < \$355,000

² \$455,000 to < \$555,000

³ \$155,000 to < \$255,000

⁴ \$55,000 to < \$75,000

⁵ \$95,000 to < \$115,000

6.70 Based on the economic model, treatment with epcoritamab was associated with an incremental cost per QALY gained of \$55,000 to < \$75,000 compared to R-GemOx. Extrapolation of the time horizon to 20 years, and the inclusion of the cure assumption at 3 years had the largest impact.

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6.71 The difference in total cost between treatment arms was primarily driven by drug costs for epcoritamab. The difference in health outcomes between treatment arms was primarily driven by the difference in time spent in the cured health state.

6.72 In the model, 76% of the incremental QALYs, 9% of the incremental drug costs, 33% of the incremental health state costs, 9% of the incremental drug acquisition costs, 11% of the incremental administration costs, and -413% of the incremental adverse event costs were accrued in the extrapolated period beyond 25.5 months.

6.73 For every patient treated with epcoritamab versus chemoimmunotherapy and followed up for 20 years, the economic evaluation (without discounting) estimated that there would be:

- An additional 3.6 years of life lived.
- An additional 2.9 years of quality-adjusted life lived.
- Additional drug costs of \$, additional drug administration costs of \$2,000, and additional health state costs of \$3,000.

6.74 The results of key sensitivity analyses are summarised in Table 18.

Table 18: Results of key sensitivity analyses

Analyses	Incremental cost	Incremental QALY	ICER	% change
Base case	\$	2.000	\$	-
Discount rate (base case: 5% costs and outcomes)				
0% costs and outcomes	\$	2.914	\$	%
3.5% costs and outcomes	\$	2.217	\$	%
Time horizon (base case: 20 years)				
5 years	\$	0.939	\$	%
10 years	\$	1.425	\$	%
15 years	\$	1.771	\$	%
30 years	\$	2.186	\$	%
OS modelling (base case: HR = 0.344)				
Unadjusted (HR = 0.512)	\$	1.408	\$	%
Tomas et al., 2023 (HR = 0.44)	\$	1.664	\$	%
PFS modelling (base case: PFS for R-GemOx derived based on OS/PFS proportionality for EPCORE NHL-1)				
Assume same HR as for OS (HR = 0.344)	\$	2.142	\$	%
Epcoritamab arm OS extrapolation (base case: log-normal)				
Log-log	\$	2.000	\$	%
Weibull	\$	2.013	\$	%
Exponential	\$	2.044	\$	%
Epcoritamab arm PFS extrapolation (base case: log-normal)				
Log-log	\$	2.023	\$	%
Gompertz	\$	2.484	\$	%
Exponential	\$	1.122	\$	%
Weibull	\$	1.859	\$	%
Epcoritamab arm adherence adjustment (base case: included ^a)				
Adherence adjustment excluded	\$	2.000	\$	%
Epcoritamab costs beyond 3 years (base case: not included) ^{b, h}				
Costs beyond 3 years included	\$	1.998	\$	%

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Analyses	Incremental cost	Incremental QALY	ICER	% change
R-GemOx arm treatment cost (base case: \$1,541.43 per 14-day cycle)				
Decrease by 50% (\$770.71 per 14-day cycle)	\$	2.000	\$ ¹	%
Subsequent treatment costs (base case: not included)				
8 cycles of R-GemOx for epcoritamab arm (\$6,165.70) ^c	\$	2.000	\$ ¹	%
Cured health state cost (base case: \$0)				
Same as progression-free state (\$233.68)	\$	2.000	\$ ¹	%
Progression-free health state utility (base case: 0.730)				
Increase by 10% (0.803)	\$	2.043	\$ ¹	%
Decrease by 10% (0.657)	\$	1.956	\$ ¹	%
Progressed disease health state utility (base case: 0.661)				
Increase by 10% (0.727)	\$	2.026	\$ ¹	%
Decrease by 10% (0.595)	\$	1.973	\$ ¹	%
Cured health state utility (base case: 0.850)				
Increase by 10% (0.935)	\$	2.129	\$ ¹	%
Decrease by 10% (0.765)	\$	1.870	\$ ¹	%
Cure assumption (base case: included; applied at 3 years)				
Applied at 2 years	\$	2.184	\$ ¹	%
Applied at 4 years	\$	1.882	\$ ⁵	%
Applied at 5 years	\$	1.810	\$ ⁵	%
Not included	\$	1.819	\$ ⁴	%
Median survival post progression (base case: 0.5 years)				
2 years	\$	2.128	\$ ¹	%
Multivariate sensitivity analyses^h				
Cure rate applied at 5 years ^d ; epcoritamab costs beyond 5 years included ^b ; 10-year time horizon ^e ; unadjusted hazard ratio for overall survival ^f .	\$ ¹	0.980	\$ ⁷	%
Cure rate applied at 5 years ^d ; epcoritamab costs beyond 5 years included ^b ; 15-year time horizon ^g ; unadjusted hazard ratio for overall survival ^f .	\$ ¹	1.187	\$ ⁷	%

Source: Compiled using the Section 3 economic model Excel workbook; Table 3-34, pp168-170 of the submission.

Abbreviations: CRS, cytokine release syndrome; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life year; R-GemOx, rituximab + gemcitabine + oxaliplatin.

^a Adherence of 96.5% assumed in Cycle 1, 96.5% in Cycles 2 to 3, 98.6% in Cycles 4 to 9 and 95.3% in Cycle 10+ based on the mean relative dose intensities reported for epcoritamab in the EPCORE NHL-1 study.

^b Extrapolated time on treatment data for epcoritamab in cells J70:J630 of the 'Markov Trace' tab copied to cells AN70:AN630 of the 'Markov Trace' tab

^c Drug costs only (no administration cost included). Applied as a one-off costs based on time to initiation of next treatment data.

^d Cell C63 of the 'Inputs Summary' tab set to 5

^e Cell C7 of the 'Inputs Summary' tab set to 10

^f Cell K46 of the 'Survival Curve Inputs' tab set to =1/L51

^g Cell C7 of the 'Inputs Summary' tab set to 15

^h Compiled during the preparation of the ESC advice

Note: Errors associated with the health state costs (annual cost of \$3,048 included in each cycle rather than 28-day cost of \$233.68), and double counting of the adverse event costs were corrected during the evaluation.

The redacted values correspond to the following ranges:

¹ \$55,000 to < \$75,000

² \$45,000 to < \$55,000

³ \$135,000 to < \$155,000

⁴ \$95,000 to < \$115,000

⁵ \$75,000 to < \$95,000

⁶ \$115,000 to < \$135,000

⁷ \$155,000 to < \$255,000

6.75 The model was most sensitive to the discount rate, the time horizon, the overall survival hazard ratio, the choice of progression-free survival extrapolation for the epcoritamab arm, inclusion of epcoritamab costs beyond 3 years and the inclusion/exclusion (and timing of application) of the cure assumption.

6.76 The ESC advised that a respecified base case incorporating the following inputs would be appropriate to address some of the concerns raised:

- Cure rate applied at 5 years (see paragraph 6.63);
- Epcoritamab costs beyond 5 years included (see paragraph 6.62);
- 10 year time horizon (see paragraph 6.68);
- Use of unadjusted hazard ratio for overall survival (0.512, see paragraph 6.60).

The ESC noted that incorporating these inputs increased the base case ICER from \$55,000 to < \$75,000 per QALY gained to \$155,000 to < \$255,000 per QALY gained.

6.77 The pre-PBAC response provided a revised base case that incorporated the following inputs:

- Cure rate applied at 5 years;
- 20 year time horizon (see paragraph 6.68);
- Use of the hazard ratio for overall survival from the Tomas et al MAIC (0.44, see paragraph 6.60).

In addition, the respecified base case incorporated epcoritamab costs in the model up to the revised cure assumption at 5 years (but not beyond), with a resulting ICER of \$95,000 to < \$115,000 per QALY gained. With the price reduction offered in the pre-PBAC response (see paragraph 3.2), the ICER reduced to \$75,000 to < \$95,000 per QALY gained.

Drug cost/patient

6.78 Table 19 presents a comparison of drug costs for epcoritamab and R-GemOx included in the economic model and financial estimates.

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Table 19: Drug cost per patient for proposed and comparator drugs

	Clinical evidence	Economic model	Financial estimates
Epcoritamab			
Dosing regimen	Priming doses of 0.16 mg and 0.8 mg on Day 1 and Day 8 of Cycle 1, respectively, prior to the full dose of 48 mg initiated on Day 15 of Cycle 1. Administered weekly during the initial 3 cycles, every 2 weeks in Cycles 4 to 9, and every 4 weeks in Cycle 10 and beyond.		
DPMA per vial ^a - 4 mg - 48 mg	-	\$ \$	\$ \$
Adherence ^b	Cycles 1-3: 96.5% Cycles 4-9: 98.6% Cycles 10+: 95.3%	Cycles 1-3: 96.5% Cycles 4-9: 98.6% Cycles 10+: 95.3%	100%
Persistence ^c	End of Year 1: 34.9% End of Year 2: 23.2%	End of Year 1: 31.8% End of Year 2: 21.0% End of Year 3: 15.4%	End of Year 1: 34.6% End of Year 2: 21.6% End of Year 3: 15.7%
4 mg vials per year ^d	-	Year 1: 1.930 Year 2+: 0	Year 1: 2 Year 2+: 0
48 mg vials per year ^e	-	Year 1: 15.152 Year 2: 3.251 Year 3: 2.191 Year 4+: 0	Year 1: 15.292 Year 2: 3.612 Year 3: 2.344 Year 4+: 0
Cost per year	-	Year 1: \$ Year 2: \$ Year 3: \$ Year 4+: \$	Year 1: \$ Year 2: \$ Year 3: \$ Year 4+: \$
Total drug costs	-	\$	\$
R-GemOx			
Dosing regimen ^f	Rituximab 375 mg/m ² IV, gemcitabine 1,000mg/m ² IV, oxaliplatin 100 mg/m ² IV on Day 1 of Cycles 1 to 8 (14-day cycles)	Rituximab: 1×500 mg vial plus 2.52×100 mg vial per cycle Gemcitabine: 1×2,000 mg vial plus 0.28×1,000 mg vial per cycle Oxaliplatin: 0.28×100 mg vial plus 1×200 mg vial per cycle	
DPMA per 14-day cycle ^h	-	Rituximab: \$448.92 Gemcitabine: \$166.67 Oxaliplatin: \$155.13	
Adherence ^g	-	100%	
Persistence ⁱ	-	After 28 days: 71.6% After 56 days: 52.2% After 84 days: 39.7% After 112 days+: 0%	
Number of 14-day cycles ^c	-	5.269	
Cost per year	-	Year 1: \$4,061 Year 2+: \$0	
Total drug costs	-	\$4,061	

Source: Constructed during the evaluation based on the Section 3 and Section 4 model Excel workbooks

Abbreviations: AEMP, approved ex-manufacturer price; DPMA, dispensed price for maximum amount; IV, intravenous; R-GemOx, rituximab + gemcitabine + oxaliplatin.

^a Based on the proposed AEMP of \$█ for epcoritamab 4 mg and \$█ for epcoritamab 48 mg; with fees and mark-ups based on a 68.41% private/31.59% public hospital split.

^b Estimates for the clinical evidence and economic model were based on the relative dose intensity by 28-day treatment cycle in the DLBCL aNHL cohort of EPCORE NHL-1. 100% adherence in the budget impact model was assumed.

^c Persistence estimates in the economic and budget impact models were calculated on a per cycle (28-day) basis based on the time to treatment discontinuation curve from the EPCORE NHL-1 study. Reported estimates for the economic model were based on estimates at the end of cycle 14 for Year 1, the end of cycle 27 for Year 2, and the end of cycle 40 for Year 3; compared to estimates for the budget impact model based on estimates at the end of cycles 13, 26 and 39, respectively.

^d Estimates account for adherence and persistence.

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^e In the economic model, drug costs were calculated over 40×28-day cycles. In the budget impact model, estimates were based on 13×28-day cycles per year, with an adjustment applied to the last cycle of each year to account for 13.04 (=365.25/28) cycles in a calendar year.

^f Based on the eviQ recommended R-GemOx treatment regimen. EPCORE NHL-1 patient level data (large B-cell lymphoma population) were used to estimate the distribution of drug costs for R-GemOx in the economic and budget impact models.

^g 100% adherence was assumed in the economic and budget impact models.

^h Based on an AEMP for rituximab of \$216.18 per 500 mg vial and \$43.24 per 100 mg vial; an AEMP for gemcitabine of \$38.74 per 2,000 mg vial and \$24.31 per 1,000 mg vial; and an AEMP for oxaliplatin of \$29.92 per 200 mg vial and \$14.97 per 100 mg vial. Fees and mark-ups based on a 68.41% private/31.59% public hospital split.

ⁱ Persistence for the R-GemOx arm based on time to treatment discontinuation for R-GemOx derived by multiplying the R-GemOx progression-free survival by the epcoritamab time on treatment divided by the epcoritamab progression-free survival.

6.79 The submission proposed an EMP of \$ [REDACTED] per induction treatment script and \$ [REDACTED] per continuing treatment script. The pre-PBAC response offered a [REDACTED] % price reduction with an EMP of \$ [REDACTED] per continuing treatment script.

Estimated PBS usage & financial implications

6.80 The submission was considered by DUSC. The submission used an epidemiological approach to estimate the utilisation and financial impacts of listing epcoritamab for the treatment of adult patients with relapsed or refractory DLBCL after two or more lines of systemic therapy.

6.81 Table 20 presents the key inputs relied on in the financial estimates.

Table 20: Key inputs for financial estimates

Parameter	Value applied and source	Comment
Incident NHL patients in Australian setting (2018-2023)	5,630 in 2018 increasing to 6,658 in 2023. AIHW Cancer data in Australia (2023) projected incidence of NHL to 2023.	DUSC agreed with the evaluation that this was reasonable.
Incident NHL patients (2024-2030)	6,868 in 2024 increasing to 8,128 in 2030. Linear extrapolation of incident patient numbers (AIHW 2023), assuming an average additional 210 patients with NHL each year (2024-2030; Year 1 to Year 6).	DUSC agreed with the evaluation that this was reasonable.
Proportion of eligible patients with DLBCL	35%; AIHW (2023), NHL incidence data stratified by histology reported 2,005 of 5,743 (35%) NHL patients with DLBCL; consistent with Leukemia Foundation Australia report (30%-40% NHL patients with DLBCL; Leukaemia Foundation, 2024).	DUSC agreed with the evaluation that this appeared reasonable.
Proportion of eligible patients with DLBCL requiring 3rd line therapy	14%. Based on advice from the sponsor's clinician advisory board.	Minutes of the clinical advisory board meeting were not provided. The estimate appeared consistent with the Kanas et al. (2022) study, which suggested 18% of NHL (DLBCL) patients in 3rd line therapy. DUSC considered this to be reasonable.
Proportion of eligible patients with DLBCL progressing to 3rd line therapy eligible for treatment with epcoritamab	87.5%. The submission assumed that the 75% of NHL (DLBCL) patients progressing to 3rd line therapy not receiving CAR-T cell therapy, would be eligible for treatment with epcoritamab. In addition, the submission assumed that 50% of the 25% of patients who received third-line CAR-T cell therapy would fail (based on Burge 2023; Jacobson 2023), and would also be eligible for treatment with epcoritamab.	DUSC agreed with the evaluation that this appeared reasonable.

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Parameter	Value applied and source	Comment
Uptake rate	Years 1-6: █████%. Assumption.	The assumption of constant uptake over time was not adequately justified and is inconsistent with the gradual uptake pattern typically observed for novel medicines. DUSC considered the constant uptake rate may be reasonable given lack of alternative options.
Grandfathered patients	Year 1: █████ ¹ ; Year 2: █████ ¹ . Sponsor data. The submission assumed all grandfathered patients had one or two prior years of treatment with epcoritamab, and would discontinue treatment in Year 2.	As for incident patients, grandfathered patients may continue epcoritamab beyond the 3rd year of treatment.
Number of epcoritamab 48 mg scripts per incident patient continuing treatment	1st year: 6.89 scripts; 2nd year: 3.61 scripts; 3rd year: 2.34 scripts. Based on the recommended epcoritamab dosing regimen, adjusted for time-on-treatment generated in the economic model, ^a assuming one script per treatment cycle of epcoritamab, and assuming patients progression free after 3 years are cured and discontinue treatment (consistent with the economic model).	The submission assumed one script per cycle for the first year of treatment (2.22 vials per script instead of 1 vial per script), which will underestimate the number of scripts (with implications for the net prescription and processing charges for Services Australia). However, the financial implications were appropriately calculated (with appropriate application of copayments, and fees and mark-ups calculated on a per vial basis). In the Australian setting, patients may continue treatment with epcoritamab beyond 3 years if progression-free, given the proposed restriction includes a stopping rule for disease progression only. The duration of treatment was therefore likely underestimated. DUSC considered the time on treatment to be reasonable however noted the potential for use beyond disease progression.
Number of R-GemOx scripts substituted by each epcoritamab patient	5.27. Based on the R-GemOx treatment regimen of 8 × 14-day cycles; adjusted for the time on treatment derived from the economic model); and one script per cycle.	The assumption that all patients treated with epcoritamab would otherwise have been treated with R-GemOx (and that R-GemOx was a reasonable proxy for all other 3rd line therapies excluding CAR-T cell therapies) was considered uncertain.
Costs for administration of epcoritamab and R-GemOx	\$101.07 per administration. MBS item 13950: Parenteral administration of one or more antineoplastic agents; Schedule fee \$118.90 (85% benefit applied).	The use of 80% of the Schedule fee is recommended in the PBAC Utilisation and Cost Model Workbook and User Manual. MBS item 13950 Schedule fee at the time of evaluation was \$123.05 (80% benefit \$98.44).

Source: Section 4.1, pp172-184 of the submission; Wellard et al (2024); IPSOS Australia DLBCL monitor Survey Report (2024), attached to the submission.

Abbreviations: AIHW, Australian Institute of Health and Welfare; ASCT, allogeneic stem cell transplant; CAR, chimeric antigen receptor; DLBCL, diffuse large B-cell lymphoma; NHL, non-Hodgkin lymphoma.

^a Adjustment for time-on-treatment initial year of treatment = [Sum of (% patients on treatment each cycle × number of vials recommended each cycle)] assuming proportion of patients on treatment in cycle 13 for the additional 0.04 cycle. Adjustment for time-on-treatment 2nd and 3rd years of treatment = [% patients on treatment in Cycle 7 mid-year each year (2nd year 27.7%; 3rd year 18.0%) × 13.04].

The redacted values correspond to the following ranges:

¹ < 500

6.82 Table 21 presents the estimated use and financial implications of listing epcoritamab on the PBS/RPBS.

Table 21: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Initiating patients treated with epcoritamab	█ ^{1a}	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Number of 4 mg scripts dispensed	█ ²	█ ²	█ ²	█ ²	█ ²	█ ²
Number of 48 mg scripts dispensed	█ ²	█ ²	█ ²	█ ²	█ ²	█ ²
Estimated financial implications of epcoritamab						
Cost to PBS/RPBS less copayments	\$█ ³	\$█ ⁴	\$█ ⁴	\$█ ⁴	\$█ ⁴	\$█ ⁴
Estimated financial implications for R-GemOx						
Cost to PBS/RPBS less copayments	-\$█ ⁵	-\$█ ⁵	-\$█ ⁵	-\$█ ⁵	-\$█ ⁵	-\$█ ⁵
Net financial implications						
Net cost to PBS/RPBS	\$█ ³	\$█ ⁴	\$█ ⁴	\$█ ⁴	\$█ ⁴	\$█ ⁴
Net cost to MBS	\$█ ⁵	\$█ ⁵	\$█ ⁵	\$█ ⁵	\$█ ⁵	\$█ ⁵
Net cost to PBS/RPBS/MBS	\$█ ³	\$█ ⁴	\$█ ⁴	\$█ ⁴	\$█ ⁴	\$█ ⁴
Pre-PBAC response						
Initiating patients treated with epcoritamab	█ ^{1a}	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Net cost to PBS/RPBS ^b	\$█ ⁴	\$█ ³	\$█ ⁴	\$█ ⁴	\$█ ⁴	\$█ ⁴
Net cost to MBS	\$█ ⁵	\$█ ⁵	\$█ ⁵	\$█ ⁵	\$█ ⁵	\$█ ⁵
Net cost to PBS/RPBS/MBS ^b	\$█ ⁴	\$█ ³	\$█ ⁴	\$█ ⁴	\$█ ⁴	\$█ ⁴

Source: Table 4-4, p178; Table 4-16, p184; Table 4-19, p186; Table 4-21, pp188; Table 4-23, p189; Table 4-26, p190 of the submission.

^a Includes 76 grandfathered patients in the first year

^b Updated to include pre-PBAC response price of \$█.

The redacted values correspond to the following ranges:

¹ < 500

² 500 to < 5,000

³ \$30 million to < \$40 million

⁴ \$40 million to < \$50 million

⁵ \$0 to < \$10 million

6.83 The estimated net cost to the PBS/RPBS of listing epcoritamab on the PBS was \$30 million to < \$40 million in Year 1, increasing to \$40 million to < \$50 million in Year 6, a total cost of \$200 million to < \$300 million over the first 6 years of listing.

6.84 The evaluation considered the estimated utilisation of epcoritamab was considered uncertain due to the following reasons:

- The assumption that all patients treated with epcoritamab who remain progression free will discontinue epcoritamab after 3 years of treatment is inconsistent with the requested listing, which includes a stopping rule for disease progression only, and may not be realised in the Australian setting. Around 15% of patients remained on epcoritamab treatment after 3 years in the economic model. In addition, retreatment with epcoritamab after relapse is not excluded in the requested restriction, but it is unclear if retreatment after third-line therapy will occur in the Australian setting. Overall, treatment duration and ongoing utilisation of epcoritamab, may be underestimated.

- The assumption of 1% uptake over the first 6 years of listing was not adequately justified and is inconsistent with the gradual uptake pattern typically observed for novel medicines.
- 6.85 DUSC considered the estimates presented in the submission may be slightly underestimated. The main issues were:
- DUSC considered that the epidemiological model is reasonable and that there may be an increase to treatment duration which may result in usage beyond expectations however noted that the sponsor was willing to address this uncertainty through an RSA. DUSC considered that disease progression in DLBCL has no formal definition and utilisation would likely continue for the duration that the disease is being controlled as opposed to achieving remission in some patients.
 - DUSC considered that a prevalent population should be included for the first year of listing.
 - DUSC considered it would be appropriate to include ECOG status into the restriction and aligning it with the trial to support evidence based practice. The PBAC noted that 94% of patients treated for relapsed or refractory DLBCL in the third line setting were reported by the submission (based on market research) to have an ECOG status of 0-2.
 - DUSC considered that leakage into second line therapy due to the relaxed definition of ‘two prior systemic therapies’ would considerably affect the financial implications and suggested that this definition could be amended to read ‘two prior systemic antineoplastic therapies, including at least 1 anti-CD20 monoclonal antibody-containing therapy’ to align with the inclusion criteria for the EPCORE NHL-1 trial.
 - DUSC noted the difficulty of accessing CAR-T cell therapy in Australia and considered that the proposed restriction would allow for most patients to bypass CAR-T cell therapy. DUSC considered that removing this requirement from the restriction would likely not substantially impact financial estimates.
- 6.86 The pre-PBAC response provided revised financial estimates that included prevalent patients in Year 1 (in addition to grandfathered patients) and that included a 5 year treatment duration to reflect the revised cure assumption in the economic model. The revised financial estimates provided in the pre-PBAC response did not incorporate the 1% price reduction offered in the response. The revised financial estimates presented in Table 21 have been updated to reflect the price reduction offered in the pre-PBAC response.

Quality Use of Medicines

- 6.87 The submission noted that a risk management plan that includes an Australian-specific annex has been submitted to the TGA. The submission stated that an epcoritamab

patient card, containing information for the patients outlining what to do if symptoms of CRS or ICANS are experienced and information for health care professionals if the patient presents for review, will be distributed to all haematologists when epcoritamab is listed on the ARTG.

- 6.88 The submission argued that there is already broad clinician experience in treating patients with epcoritamab in Australia, given that 30 centres have participated in epcoritamab clinical trials and |centres via the compassionate access program.
- 6.89 Based on advice from an Australian haematology expert steering committee, the following quality use of medicine activities will be implemented:
- Education on the unique treatment considerations and specific requirements for epcoritamab.
 - Education on risk stratification, including predicting risk during priming doses and first and second full doses.
 - Development of educational material for treatment sites including standard operating procedures, and an onboarding training program with centre-specific adaptations across regional, public and private centres.
 - Development of educational materials for patients and caregivers, including CRS awareness and empowering self-advocacy if/when presenting with CRS symptoms
 - A product reconstitution pamphlet included in every carton of epcoritamab 4mg vial.
 - Availability of the sponsor's Medical Information Service Line.
 - Development of CRS/ICANS treatment guidelines.
 - Ensuring availability of tocilizumab at treatment centres.
 - Recommendation of a primary point of contact designated at each site to initiate optimal multi-disciplinary team management for adverse event presentations.
- 6.90 The submission stated that the sponsor is planning a phase 4, international study to investigate outcomes for patients treated with epcoritamab treatment in patients in third or later-line large B-cell lymphoma in a real-world setting. The study is planned to start in Q2 2025, with a global study requirement that the product must be broadly available (i.e. PBS listed) for the inclusion of Australian sites. Efficacy outcomes will include overall response rate, complete response, duration of response progression-free survival, overall survival and time to next treatment. Additional exploratory objectives include health-related quality of life, healthcare utilisation, and treatment patterns. Safety data will also be collected as part of standard clinical trial pharmacovigilance.

Financial Management – Risk Sharing Arrangements

- 6.91 The submission stated that the sponsor is willing to enter into a risk sharing arrangement based on the financial estimates included in the submission, to address any perceived uncertainty in estimating the overall cost to the PBS.

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

7 PBAC Outcome

- 7.1 The PBAC recommended the listing of epcoritamab for the treatment of patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL). The PBAC is satisfied that epcoritamab provides, for some patients, a significant improvement in efficacy over rituximab + gemcitabine + oxaliplatin (R-GemOx), as a proxy for rituximab-based chemoimmunotherapy treatments. The PBAC's recommendation for listing was based on, among other matters, its assessment that the cost-effectiveness of epcoritamab would be acceptable with a price reduction to achieve an acceptable incremental cost-effectiveness ratio (ICER) using the pre-PBAC response economic model amended to include a revised hazard ratio for overall survival, and with a risk sharing arrangement to address concerns regarding the potential for use outside of the proposed restriction.
- 7.2 The PBAC noted the input from health care professionals, Rare Cancers Australia and Leukaemia Foundation that highlighted the need for more treatment options for relapsed or refractory DLBCL. The PBAC noted the comments from the clinician at the sponsor hearing that, for complex reasons, not all eligible patients for CAR-T cell therapy were accessing such therapy. The PBAC noted the consumer comments also highlighted the potential quality of life benefits of treatments that can be delivered outside of metropolitan hospitals. The PBAC acknowledged the high clinical need for additional treatments for this condition that has a very poor prognosis.
- 7.3 With regard to the requested listing and restriction, the PBAC advised that:
- As per paragraph 3.3, the PBAC considered a dual Section 100 (Efficient Funding of Chemotherapy - Related Benefits) and General Schedule listing was appropriate.
 - An Authority Required (Telephone) listing rather than an Authority Required (STREAMLINED) listing was appropriate for both the Induction and Grandfathering treatment restrictions given epcoritamab is a new chemical entity and a first in class medicine for which there is not prior experience on the PBS. The Committee considered that an Authority Required (STREAMLINED) listing was appropriate for the Continuing treatment restriction.
 - As per paragraph 3.4, the treatment criteria proposed by the Secretariat regarding the number of repeats for the Continuing and Grandfathering treatment restrictions was appropriate.

- The clinical criteria regarding chimeric antigen receptor-T (CAR-T) cell therapy are appropriate and should remain in the restriction. In addition, the PBAC considered the clinical criteria stating ‘the condition must have relapsed, or be refractory to, at least two prior systemic therapies’ was appropriate.
 - As outlined by the DUSC in paragraph 6.85, the PBAC considered the restriction should include a requirement for patients to have an ECOG performance status of 0-2.
 - A caution regarding the need for careful monitoring of patients due to risk of developing life-threatening Cytokine Release Syndrome (CRS) should be included in the restriction.
 - A grandfathering restriction was appropriate for continuing treatment (i.e. for patients who have completed induction treatment).
- 7.4 The PBAC considered that R-GemOx, as a proxy for rituximab-based chemoimmunotherapy treatments used for the management of relapsed or refractory DLBCL, was an appropriate comparator.
- 7.5 The pivotal evidence for epcoritamab was derived from the EPCORE NHL-1 study, an ongoing, phase 1/2, open-label, single-arm study of epcoritamab monotherapy. The PBAC noted that the overall response rate among patients treated with epcoritamab was 61.9% (independent review committee-assessed), including a complete response rate of 40.3% (April 2023 data cut (n=139)), with an overall response rate of 59% (investigator-assessed) reported at the May 2024 data cut (n=157). The PBAC noted that at the May 2024 data cut the median investigator-assessed progression-free survival was 37.3 months (95% CI: 26.0, not estimable) for patients who achieved a complete response and 4.2 months (95% CI: 2.8, 5.5) for all patients treated with epcoritamab. Likewise, the PBAC noted that at a median 37.1 months follow-up, the median overall survival was 18.5 months (95% CI: 11.7, 27.7) for all patients treated with epcoritamab and not reached (95% CI: 36.4 months, not estimable) among patients who achieved a complete response. The PBAC also noted that 63% of complete responders were alive at 36 months. The PBAC agreed with the ESC that the EPCORE NHL-1 study results provided indicated that complete responses were being maintained in the context of an aggressive lymphoma.
- 7.6 The PBAC noted the clinical claim of superior effectiveness was based on an unanchored matching adjusted indirect comparison (MAIC) of efficacy outcomes for epcoritamab (EPCORE NHL-1) versus chemoimmunotherapy/chemotherapy in patients with no prior CAR-T cell therapy (SCHOLAR-1 study). The PBAC considered the MAICs were associated with a substantial amount of uncertainty due to the low effective sample size after matching, the potential for bias due to failure to match all relevant prognostic and treatment effect modifier variables, the uncertain applicability of the Neelapu et al. (2021) analysis of the SCHOLAR-1 study, and the unclear impact of the truncation of adjustment weights on the results. The PBAC noted the PSCR provided a MAIC based on the data included in the original Crump et al.

(2017) SCHOLAR-1 study publication and agreed with the ESC that it did not substantially change the clinical outcomes seen in the original MAIC, nor did it address the concerns regarding the uncertainty of the MAICs. The PBAC considered that this uncertainty was also not addressed by the MAICs provided as supportive evidence (Iacoboni et al., 2024; Tomas et al., 2023). The PBAC noted the ESC advice that the results of the EPCORE DLBCL-1 trial would likely be informative in addressing concerns regarding the magnitude of clinical benefit. However, the PBAC was concerned that the EPCORE DLBCL-1 trial was for a different line of therapy and was not anticipated to read out for at least another 12 to 18 months (see paragraph 2.2). Overall, acknowledging the limitations of the SCHOLAR study, the PBAC agreed with the ESC that it can be considered representative of third-line DLBCL treatment. As such, the PBAC considered that although uncertain, the MAIC of epcoritamab (EPCORE NHL-1) versus chemoimmunotherapy/chemotherapy (SCHOLAR-1 study) provided the best available evidence for assessing the claim of superior clinical effectiveness. The PBAC considered that the claim of superior comparative effectiveness was reasonable, but agreed with the ESC that the magnitude of the clinical benefit could not be reliably estimated from the evidence presented.

- 7.7 The clinical claim of non-inferior safety was based on a naïve comparison of adverse event outcomes for the EPCORE NHL-1, CORAL and LY.12 studies. Only selected adverse events were reported in the publications for the CORAL and LY.12 studies, and there was insufficient overlap in the reported adverse events to allow for a robust comparison between studies. The PBAC agreed with the ESC that the safety profiles of epcoritamab and chemoimmunotherapy were different. The PBAC considered that claim of non-inferior comparative safety was uncertain based on the evidence presented, but may be reasonable.
- 7.8 The submission presented a cost-utility analysis to determine the cost-effectiveness of epcoritamab with the base case reporting an ICER of \$55,000 to < \$75,000 per QALY gained. The base case used the adjusted hazard ratio (HR = 0.344) derived from the unanchored MAIC of epcoritamab (EPCORE NHL-1) versus chemoimmunotherapy /chemotherapy (SCHOLAR-1) to model overall survival, assumed a cure for all patients remaining progression-free at 3 years with all patients ceasing treatment with epcoritamab at that time, and incorporated a 20 year time horizon. The PBAC noted the matching of selected variables in the adjusted MAIC was associated with a substantial improvement in survival outcomes for epcoritamab compared to the unadjusted MAIC. Given the uncertainty in the evidence base the PBAC was less confident that the lower point estimate for the adjusted hazard ratio accurately reflected the efficacy of epcoritamab. The PBAC noted the ESC advice that the use of the unadjusted MAIC hazard ratio may be more appropriate for modelling overall survival. The ESC also considered a cure assumption at 3 years was highly uncertain given the lack of data available to inform long term outcomes associated with epcoritamab treatment. The PBAC noted the ESC proposed a revised base case with a cure rate applied at 5 years, epcoritamab costs beyond 5 years included, use of the

unadjusted MAIC hazard ratio (HR = 0.512) and a 10 year time horizon. Incorporating these inputs increased the base case ICER to \$155,000 to < \$255,000 per QALY gained. The PBAC noted the pre-PBAC response proposed a revised base case that accepted the application of a cure rate at 5 years but excluded epcoritamab costs beyond that point, included the hazard ratio for overall survival from the Tomas et al MAIC (HR = 0.44) and retained a 20 year time horizon. The PBAC noted that with the price reduction offered in the pre-PBAC response (see paragraph 3.2) the resulting ICER was \$75,000 to < \$95,000 per QALY gained, which the Committee considered high and uncertain. The PBAC did not accept the pre-PBAC response argument for the use of the hazard ratio for overall survival from the Tomas et al MAIC and instead agreed with the ESC that the use of the unadjusted MAIC hazard ratio was appropriate to address some of the uncertainty in the overall survival outcomes.

- 7.9 The PBAC considered that with the inclusion of the unadjusted MAIC hazard ratio (HR = 0.512) the pre-PBAC response revised base case with a 20 year time horizon, a cure rate applied at 5 years and epcoritamab costs excluded beyond that point could be used to establish the cost-effectiveness of epcoritamab. The PBAC advised that an ICER in the order of \$75,000 to < \$95,000 per QALY was appropriate and considered that a price reduction would be required to achieve cost-effectiveness.
- 7.10 The PBAC noted the pre-PBAC response provided revised financial estimates that included a 5 year treatment duration to reflect the revised cure assumption in the economic model and the addition of a prevalent patient population in Year 1. The PBAC noted the addition of the prevalent patient population was consistent with DUSC advice. However, the PBAC considered the inclusion of both a prevalent patient population and a separate grandfathered population was not appropriate as the latter would already be accounted for in the prevalent patient population. The PBAC advised that the separate grandfathered population be removed from the revised financial estimates provided in the pre-PBAC response. As outlined in paragraph 7.3, the PBAC agreed with the DUSC that ECOG performance status should be included in the restriction. Consistent with this, the PBAC advised that ECOG performance status should also be accounted for in the financial estimates by assuming that 94% of patients treated for relapsed or refractory DLBCL in the third-line setting have an ECOG score of 0-2 (see paragraph 6.85). Overall, the PBAC considered that the revised financial estimates presented in the pre-PBAC response should be amended to remove grandfathered patients, account for ECOG performance status and be updated with the outcomes from the recommendations made by the Committee in paragraph 7.8. The PBAC considered the resulting financial estimates would be appropriate to form the basis of a risk sharing arrangement.
- 7.11 The PBAC agreed with the DUSC that there was a risk of use outside of the proposed restriction as second-line therapy. The PBAC considered that a risk sharing arrangement with a $\frac{1}{2}$ % rebate above the financial caps would be appropriate to mitigate the potential impact to the Commonwealth of use beyond the restriction and any residual uncertainty around the duration of treatment.

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- 7.12 The PBAC recommended that epcoritamab should not be treated as interchangeable with any other drugs.
- 7.13 The PBAC advised that is not suitable for prescribing by nurse practitioners.
- 7.14 The PBAC recommended that the Early Supply Rule should not apply.
- 7.15 The PBAC found that the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met. Specifically the PBAC found that in the circumstances of its recommendation for epcoritamab:
- The treatment is not expected to provide a substantial and clinically relevant improvement in efficacy over R-GemOx, as, while clinically relevant, the magnitude of the clinical benefit could not be reliably estimated from the evidence presented;
 - The treatment is expected to address a high and urgent unmet clinical need;
 - It was not necessary to make a finding in relation to whether it would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A because one or more of the preceding tests had failed.
- 7.1 The PBAC advised that this submission is not eligible for an Independent Review as it received a positive PBAC recommendation.

Outcome:

Recommended

8 Recommended listing

8.1 Add new item:

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
EPCORITAMAB					
epcoritamab 4 mg/0.8 mL injection, 0.8 mL vial	NEW (CT)	1	1	1	Epkinly
epcoritamab 4 mg/0.8 mL injection, 0.8 mL vial	NEW (GE)	1	1	1	Epkinly
Category / Program: <input checked="" type="checkbox"/> Section 100 – Efficient Funding of Chemotherapy – <i>Related Benefits (Code CT)</i> <input checked="" type="checkbox"/> <i>General Schedule (Code GE)</i>					
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners					
Benefit type: <input checked="" type="checkbox"/> Authority Required (immediate assessment): Telephone/Online					
Restriction type: <input checked="" type="checkbox"/> Non-complex Authority Required (non-CAR)					
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 888 333.					
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.					

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	Caution: Careful monitoring of patients is required due to risk of developing life-threatening Cytokine Release Syndrome (CRS).
Restrictions Summary [new1] / Treatment of Concept: [new1A]	
	Episodicity: [Blank]
	Severity: Relapsed or refractory
	Condition: Diffuse large B-cell lymphoma (DLBCL)
	Indication: Relapsed or refractory Diffuse large B-cell lymphoma (DLBCL)
	Treatment Phase: Induction treatment
	Clinical criteria:
	The condition must have relapsed, or be refractory to, at least two prior systemic therapies,
	AND
	Clinical criteria:
	Patient must have a WHO performance status no higher than 2
	AND
	Clinical criteria:
	Patient must have previously received treatment with chimeric antigen receptor-T (<i>CAR-T</i>) cell therapy for this condition; OR
	Patient must be currently unable to receive treatment with <i>CAR-T</i> cell therapy for this condition.
	AND
	Clinical criteria:
	Patient must not be eligible for stem cell transplantation
	AND
	Clinical criteria:
	The treatment must be discontinued in patients who experience disease progression whilst on treatment.
	Prescribing Instructions: Prior systemic therapy may include autologous stem cell transplant.
	Prescribing Instructions: For the purposes of the restriction, the definition of patients unable to receive treatment with <i>CAR-T</i> cell therapy for this condition include: geographical access barriers, psychosocial reasons, and clinical ineligibility or urgency.
	Administrative Advice: A dose of 0.16mg to be administered on Day 1 with initial 4mg vial. A dose of 0.8mg to be administered on Day 8 with the repeat 4mg vial. Refer to the Epcoritamab TGA Product Information.

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
EPCORITAMAB					
epcoritamab 48 mg/0.8 mL injection, 0.8 mL vial	NEW (CT)	1	1	9	Epinkly
epcoritamab 48 mg/0.8 mL injection, 0.8 mL vial	NEW (GE)	1	1	9	Epinkly
	Category / Program:				
	<input checked="" type="checkbox"/> Section 100 – Efficient Funding of Chemotherapy – <i>Related Benefits (Code CT)</i>				
	<input checked="" type="checkbox"/> <i>General Schedule (Code GE)</i>				
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners				
	Restriction type: <input checked="" type="checkbox"/> Authority Required (STREAMLINED)				
	Administrative Advice: Special pricing arrangements apply.				
	Administrative Advice: No increase in the maximum quantity or number of units may be authorised.				

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	Administrative Advice: No increase in the maximum number of repeats may be authorised.
	Caution: Careful monitoring of patients is required due to risk of developing life-threatening Cytokine Release Syndrome (CRS).
Restrictions Summary [new2] / Treatment of Concept: [new2A]	
	Episodicity: [Blank]
	Severity: Relapsed or refractory
	Condition: Diffuse large-B-cell lymphoma (DLBCL)
	Indication: Relapsed or refractory Diffuse large B-cell lymphoma (DLBCL)
	Treatment Phase: Continuing treatment
	Clinical criteria:
	Patient must have previously received PBS-subsidised treatment with this drug for this condition,
	AND
	Clinical criteria:
	The treatment must be discontinued in patients who experience disease progression whilst on treatment.
	AND
	Treatment criteria:
	Patient must be undergoing treatment with this drug administered weekly in cycles 1-3 – prescribe up to 9 repeats; OR
	Patient must be undergoing treatment with this drug administered fortnightly in cycles 4-9 – prescribe up to 5 repeats; OR
	Patient must be undergoing treatment with this drug administered every four weeks in cycles 10 and beyond – prescribe up to 2 repeats

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
EPCORITAMAB					
epcoritamab 48 mg/0.8 mL injection, 0.8 mL vial	NEW (CT)	1	1	9	Epkinly
epcoritamab 48 mg/0.8 mL injection, 0.8 mL vial	NEW (GE)	1	1	9	Epkinly
	Category / Program:				
	<input checked="" type="checkbox"/> Section 100 – Efficient Funding of Chemotherapy – Related Benefits (Code CT)				
	<input checked="" type="checkbox"/> General Schedule (Code GE)				
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners				
	Benefit type: <input checked="" type="checkbox"/> Authority Required (immediate assessment): Telephone/Online				
	Restriction type: <input checked="" type="checkbox"/> Non-complex Authority Required (non-CAR)				
	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 888 333.				
	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.				
	Caution: Careful monitoring of patients is required due to risk of developing life-threatening Cytokine Release Syndrome (CRS).				
Restrictions Summary [new3] / Treatment of Concept: [new3A]					
	Episodicity: [Blank]				
	Severity: Relapsed or refractory				
	Condition: Diffuse large-B-cell lymphoma (DLBCL)				

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	Indication: Relapsed or refractory Diffuse large B-cell lymphoma (DLBCL)
	Treatment Phase: Transitioning from non-PBS to PBS-subsidised treatment - Grandfathering treatment
	Clinical criteria:
	Patient must have received non-PBS subsidised treatment with this drug for this PBS condition prior to [PBS listing date]
	AND
	Clinical criteria:
	The condition must have relapsed, or be refractory to, at least two prior systemic therapies, prior to commencing treatment with this drug
	AND
	Clinical criteria:
	Patient must have a WHO performance status no higher than 2 prior to commencing treatment with this drug for this condition
	AND
	Clinical criteria:
	Patient must have previously received treatment with chimeric antigen receptor-T (CAR-T) cell therapy for this condition; or
	Patient must have been unable to receive treatment with CAR-T cell therapy for this condition.
	AND
	Clinical criteria:
	Patient must not be eligible for stem cell transplantation.
	AND
	Clinical criteria:
	The treatment must be discontinued in patients who experience disease progression whilst on treatment.
	AND
	Treatment criteria:
	Patient must be undergoing treatment with this drug administered weekly in cycles 1-3 – prescribe up to 9 repeats; OR
	Patient must be undergoing treatment with this drug administered fortnightly in cycles 4-9 – prescribe up to 5 repeats; OR
	Patient must be undergoing treatment with this drug administered every four weeks in cycles 10 and beyond – prescribe up to 2 repeats
	Prescribing Instructions: Prior systemic therapy may include autologous stem cell transplant.
	Prescribing Instructions: For the purposes of this restriction, the definition of patients unable to receive treatment with CAR-T cell therapy for this condition include: geographical access barriers, psychosocial reasons, and clinical ineligibility or urgency.
	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.

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

9 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.

10 Sponsor's Comment

The sponsor had no comment.