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SMC2881

epcoritamab solution for injection (Tepkinly®)

AbbVie

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The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission assessed under the orphan equivalent medicine process **epcoritamab (Tepkinly®)** is accepted for use within NHSScotland.

Indication under review: as monotherapy for the treatment of adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy.

In a single-arm, open-label, phase II study, treatment with epcoritamab was associated with an overall response rate of 82%. Indirect comparisons suggested improvements in overall survival and progression-free survival with epcoritamab compared with current care.

This advice applies only in the context of an approved NHSScotland Patient Access Scheme (PAS) arrangement delivering the cost-effectiveness results upon which the decision was based, or a PAS/ list price that is equivalent or lower.

This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting.

Chair
Scottish Medicines Consortium

1. Clinical Context

1.1. Medicine background

Epcoritamab is a bispecific antibody that binds to a specific extracellular epitope of CD20 on B cells and to CD3 on T cells. The activity of epcoritamab is dependent on simultaneous engagement of CD20-expressing cancer cells and CD3-expressing endogenous T cells, which induces specific T-cell activation and T-cell-mediated killing of CD20-expressing cells. [1]

It is administered by subcutaneous injection in 28-day cycles and should be administered until disease progression or unacceptable toxicity. Dosing begins with a step-up dosing schedule leading to the recommended full dose of 48 mg, administered weekly (cycles 1 to 3); every two weeks (cycles 4 to 9) and every four weeks (from cycle 10 onwards). For full information on administration of epcoritamab, including recommended premedication / prophylaxis treatment and epcoritamab dose step-up schedule, refer to Summary of Product Characteristics (SPC). [1]

1.2. Disease background

Follicular lymphoma (FL) is an incurable, non-Hodgkin's lymphoma (NHL). Although the disease is heterogeneous, for many people it is chronic with spontaneous episodes of relapse and a relatively long overall survival. Common symptoms include swelling of lymph nodes, fatigue, unexplained weight loss, night sweats or fevers; however, many patients are asymptomatic. After increasing numbers of relapses, the disease-free intervals and duration of response become shorter and the risk of refractoriness to treatment increases. The median progression-free survival (PFS) for patients who have received two prior therapies is approximately 1 year and median overall survival ranges from approximately 5 to 9 years; estimates vary across different sources. [2-5]

1.3. Treatment pathway and relevant comparators

For patients with relapsed or refractory (R/R) FL, there is no standard treatment, and options depend on patient fitness and choice, prior therapy and R/R status. Options include obinutuzumab plus bendamustine followed by obinutuzumab maintenance (SMC 1219/17), for rituximab-refractory cases or early relapse. Retreatment with the same rituximab chemotherapy regimen may be considered if the initial remission was prolonged; if the remission was shorter an alternative rituximab chemotherapy regimen may be considered. Chemotherapy regimens used in combination with rituximab include cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP), bendamustine, or cyclophosphamide, vincristine and prednisolone (R-CVP). Rituximab plus lenalidomide (SMC2281) is an alternative option and may be appropriate for selected patients, especially for those with short remissions after chemotherapy or in whom chemotherapy is poorly tolerated. Eligible patients may also be considered for autologous stem cell transplant or entry into available clinical trials. Idelalisib (SMC 1039/15) can be used for patient's refractory to two prior treatment lines; however, clinical experts advised that use in Scotland has declined due to its toxicity profile. [2-4]

More recently, chimeric antigen receptor T-cell (CAR-T) treatments, tisagenlecleucel (after two or more prior therapies) and axicabtagene ciloleucel (after three or more treatment lines) were licensed in R/R FL; however, these were not recommended by SMC in the absence of submissions from the marketing authorisation holders (SMC2566 and SMC2646). The bispecific monoclonal

antibody mosunetuzumab and the Bruton's tyrosine kinase inhibitor zanubrutinib, both licensed for use after two or more prior systemic therapies, were not recommended by SMC following a full submission (SMC2542) and in the absence of a submission (SMC2671), respectively.

Cancer Medicines Outcome Programme Public Health Scotland (CMOP-PHS) data indicate that the most commonly prescribed regimen was rituximab plus lenalidomide (used in approximately a third of patients), followed by R-CHOP (used in approximately a fifth of patients), with a range of other regimens (including bendamustine with obinutuzumab, and bendamustine with rituximab) used less frequently. [6]

The submitting company considers a basket of chemoimmunotherapy and chemotherapy treatments as the most relevant comparator for this submission.

1.4. Category for decision-making process

Eligibility for interim acceptance decision option

Epcoritamab has conditional marketing authorisation from the Medicines and Healthcare products Regulatory Agency.

Eligibility for a PACE meeting

Epcoritamab meets SMC orphan equivalent criteria for this indication.

2. Summary of Clinical Evidence

2.1. Evidence for the licensed indication under review

Evidence to support the efficacy and safety of epcoritamab for this indication comes from the EPCORE NHL-1 study. Data from the patients with FL from the expansion part of the study were presented in the submission, details of which are presented in Table 2.1.

Table 2.1. Overview of relevant study[2, 7, 8]

Criteria	EPCORE NHL-1
Study design	Ongoing, international, open-label, multi-cohort, single arm, phase I/II study. Details below relate only to the group of patients with FL in the indolent NHL cohort from the dose expansion part of the study.
Eligible patients	• Adults with documented CD20+ mature B-cell neoplasm according to WHO classification 2016 or WHO classification 2008: histologic confirmed FL grade 1, 2 or 3A at initial diagnosis without clinical or pathological evidence of transformation. • R/R disease and previously treated with at least two lines of systemic antineoplastic therapy including at least one anti-CD20 monoclonal antibody-containing therapy. Relapsed disease was defined as disease that has recurred ≥6 months after completion of therapy. Refractory disease is defined as disease that either progressed during therapy or progressed within 6 months of completion of therapy. • Previously treated with an alkylating agent or lenalidomide. • R/R to the last prior line therapy. Previous lymphoma therapy is defined as one of the following: at least 2 months of single-agent therapy, at least two consecutive cycles of combination therapy, autologous HSCT, immunomodulatory therapy or radio immunotherapy. • Patients must have had measurable disease.

	• ECOG performance status of 0 to 2.
Treatments	Dose expansion: Epcoritamab was administered by subcutaneous injection in 28-day cycles. In cycle 1, step-up dosing consisted of 0.16 mg on day 1, followed by 0.8 mg on day 8 and subsequent 48 mg doses on day 15 and thereafter until disease progression or unacceptable toxicity. Epcoritamab was administered once weekly during cycles 1 to 3, every 2 weeks during cycles 4 to 9 and every 4 weeks from cycle 10. Patients received premedication for CRS 30 to 120 minutes before the first four doses of epcoritamab (optional for subsequent doses).
Primary outcome	ORR*, defined as the proportion of patients who achieved a best overall response of complete response or partial response at any time.
Selected secondary outcomes	• DOR*: defined as the time from the first documentation of response (CR or PR) to the date of disease progression or death, whichever occurs earlier. • CR rate*, defined as the proportion of patients with CR. • PFS*: defined as the time from day 1 of cycle 1 to first documented disease progression or death due to any cause, whichever occurs earlier. • OS, defined as the time from day 1 of cycle 1 to death.
Statistical analysis	No formal statistical hypotheses were formulated.

*determined by Lugano response assessment criteria as assessed by IRC

Abbreviations: CR = complete response; CRS = cytokine release syndrome; DOR = duration of response; ECOG = Eastern Cooperative Oncology Group; FL = follicular lymphoma; HSCT = haematopoietic stem cell transplantation; IRC = independent review committee; NHL = non-Hodgkin's lymphoma; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PR = partial response; R/R = relapsed or refractory; WHO = World Health Organisation.

At the primary analysis (data cut off 21 April 2023), the ORR was 82% in FL patients with 62% of patients in CR. At the most recent data cut off, the ORR was similar. [2, 7 8] The submitting company noted that survival outcomes from the dose expansion cohort may have been adversely affected by COVID-19-related mortality during the pandemic. To explore this, post-hoc analyses were provided in which deaths attributed to COVID-19 were censored, with the aim of better reflecting the current clinical landscape and expected outcomes for epcoritamab. Key results are presented in Table 2.2.

Table 2.2. Key efficacy results for the patients with FL in EPCORE NHL-1 expansion cohort [2, 7, 8]

	Primary analysis - data cut off 21 April 2023 (n=128)
Primary outcome: ORR (IRC-assessed, Lugano criteria)	
ORR (CR+PR), %	82%
• CR, %	62%
• PR, %	20%
Secondary outcome: DOR (IRC-assessed, Lugano criteria)	
Median DOR, months	NR
Secondary outcome: PFS (IRC-assessed, Lugano criteria)	
Events, n	55
Median PFS, months	15.4 months
PFS rate at 21 months	49%
PFS rate at 24 months	-
Secondary outcome: OS	
Median OS follow-up, months	17.4 months
Deaths	34
Median OS	NR
OS rate at 18 months	70%

Abbreviations: CI = confidence interval; CR = complete response; DOR = duration of response; IRC = independent review committee; NR = not reached; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PR = partial response.

*Other data were also assessed but remain confidential.**

2.2. Health-related quality of life outcomes

Health Related Quality of Life (HRQoL) was assessed using FACT-Lym, a questionnaire to assess the quality of life in patients with lymphoma, consisting of a general quality of life instrument (FACT-G) and a condition-specific module (Lym), and EQ-5D-3L, a questionnaire designed to assess health status in adults.

Overall, the data suggest that epcoritamab was associated with no worsening of symptoms or quality of life in patients with FL, indicating maintained HRQoL. [2]

2.3. Supportive studies

Following the dose expansion phase of EPCORE NHL-1, a dose optimisation phase was conducted to evaluate alternative step-up dosing regimens aimed at reducing the risk and severity of cytokine release syndrome (CRS). One cohort included patients with FL, in whom two regimens were initially evaluated (n=6 per arm). The regimen incorporating an additional 3 mg intermediate step-up dose on day 15 (before the first 48 mg full dose on day 22) was associated with a lower CRS rate, was subsequently expanded (n=86), and represents the licensed dosing regimen. [7, 8]

The primary objectives of the optimisation phase concerned safety; however, some efficacy data were collected. [2, 7, 8] At the primary analysis with data cut off 8 January 2024, with a median follow-up of 5.7 months, the ORR was 86% in FL patients with 64% of patients in CR.[7] The submitting company presented results from a later data cut off (9 December 2024).[9] Survival outcomes from this data cut off of the dose optimisation phase, started after the peak of COVID-19, were used to support use of the COVID-modified outcomes from the dose expansion cohort in the economic base case.

*Other data were also assessed but remain confidential.**

2.4. Indirect evidence to support clinical and cost-effectiveness comparisons

In the absence of direct comparative evidence, the submitting company conducted an indirect treatment comparison to assess the effectiveness of epcoritamab versus current care in adults with R/R FL treated in the third line or later (3L+) setting. An unanchored matching adjusted indirect comparison (MAIC) was conducted, as no common comparator was available. Individual patient data from the FL dose expansion cohort of the EPCORE NHL-1 trial provided the evidence for epcoritamab.[7] Comparator data were obtained from the Haematological Malignancy Research Network (HMRN), a UK population based real world evidence dataset, which was used as an external control.[10] Given the lack of a single standard treatment in the 3L+ setting and the heterogeneity of management in routine practice, the comparator was defined as a basket of chemoimmunotherapy and chemotherapy regimens. The MAIC reweighted the EPCORE NHL-1 population to align with the HMRN cohort for selected prognostic factors and treatment effect modifiers (10 covariates). The MAIC assessed overall survival (OS) and progression free survival (PFS), which were also used to inform the economic base case analysis.

Table 2.3. Summary of indirect treatment comparison

Criteria	Overview
Design	Unanchored MAIC.
Population	Adults with R/R FL treated in the third line or later setting.
Comparators	Epcoritamab compared with current care, described by the submitting company as a basket of chemotherapy and chemoimmunotherapy regimens, which they consider to be represented by the HMRN dataset.
Studies included	EPCORE NHL-1[7] (data for epcoritamab; R/R 3L+ FL expansion cohort): international, open-label, single arm, phase I/II study HMRN[10] dataset (data for R/R 3L+ FL): population based real world evidence cohort
Outcomes	OS, PFS
Results	The evidence suggests that epcoritamab has superior efficacy to current 3L+ care in both the unadjusted and adjusted analyses for OS and PFS.

Abbreviations: CI = confidence interval; HMRN = Haematological Malignancy Research Network; HR = hazard ratio; 3L+ = third line or later treatment; MAIC = matching adjusted indirect comparison; OS = overall survival; PFS = progression free survival; R/R FL = relapsed or refractory follicular lymphoma.

*Other data were also assessed but remain confidential.**

3. Summary of Safety Evidence

Evidence from EPCORE NHL-1 study supports the safety of epcoritamab for the treatment of patients with R/R FL, who have received at least two prior therapies. However, there are no comparative safety data available. The company's indirect treatment comparison did not compare safety outcomes with the relevant comparators.

A pooled safety analysis included patients who received the full 48 mg dose from the dose escalation and expansion parts of the EPCORE NHL-1 study, comprising 129 patients with FL. As of data cut off 21 April 2023, with a median follow-up of 17.4 months, the median duration of treatment in the pooled FL group was 8.3 months. [2, 7]

Any treatment-emergent adverse event (AE) was reported by 98% (127/129) of patients and these were considered possibly treatment-related in 93%. Patients reporting a grade 3 or higher AE were 69% (including 37% treatment-related), patients with a reported serious AE were 69% (including 46% treatment-related), the proportion of AEs that led to dose delay was 60% (including 35% treatment-related) and to discontinuing therapy was 19% (including 3.9% treatment-related).[2]

The most frequently reported treatment-emergent AEs with an incidence >20% in the pooled FL group (n=129) were CRS (67%), injection site reaction (36%), COVID-19 (31%), fatigue (30%), diarrhoea (36%), pyrexia (25%), and neutropenia (20%). [2]

The most frequently reported treatment-related AEs of any grade with an incidence >10% in the pooled FL group (n=129) were CRS (67%), neutropenia (19%), fatigue (19%), injection site erythema (17%), pyrexia (12%), and diarrhoea (11%). [2]

The safety profile of epcoritamab in R/R FL was considered to be in line with its known safety profile and with expectations for a CD3/CD20 bispecific T-cell engager. Expected mechanism of action-related events, including CRS, immune effector cell-associated neurotoxicity syndrome (ICANS), clinical tumour lysis syndrome, cytopenias and infections, were observed. Overall safety appears acceptable with appropriate monitoring in this advanced, heavily pretreated population, although the non-comparative study design and limited dataset mean additional data are required

in the context of a conditional marketing authorisation. The revised posology tested in the optimisation cohort showed a comparable safety profile with no new concerns and a clinically relevant reduction in Grade 2 CRS, supporting inclusion of the 3-step step-up dosing regimen and CRS management recommendations in the SPC.[2]

4. Summary of Clinical Effectiveness Considerations

4.1. Key strengths

- Clinically meaningful overall and complete response rates were demonstrated in patients with R/R FL following two or more prior systemic therapies. [2]

4.2. Key uncertainties

- Key evidence is from a cohort of EPCORE NHL-1, a single-arm, open-label study. The design hinders the interpretation of results. In addition, there was no formal statistical testing for any of the outcomes.
- To assess the relative efficacy of epcoritamab compared with current 3L+ care in R/R FL, the submitting company conducted an unanchored MAIC, which suggested improved OS and PFS. However, it is subject to several limitations. Estimates varied depending on analytical assumptions. The comparison is unanchored and relies on a small cohort from a single arm, open-label, phase I/II study compared with real world data, increasing susceptibility to residual confounding. Key prognostic variables were not included due to reporting limitations in the HMRN dataset. In addition, epcoritamab survival data remain immature, and the MAIC analysis relies on uncertain post-hoc COVID-modified survival estimates. Survival estimates observed in the HMRN comparator dataset appear considerably lower than previously reported for the population of interest. The HMRN treatment mix may not be fully representative of Scottish practice, where a higher proportion of patients might be expected to receive rituximab plus lenalidomide, which may be associated with better outcomes than some of the treatments included in the HMRN dataset. Due to these limitations, the MAIC results are associated with considerable uncertainty.
- Follow-up duration in the relevant cohort of EPCORE NHL-1 was limited. At the primary analysis data cut (21 April 2023), median OS follow-up was 17.4 months. Confidential data from a later data cut off extended the median OS follow-up. Median OS had not been reached at any reported data cut.[11] Long-term efficacy and safety remain uncertain. The submitting company notes that the dose-expansion part of EPCORE NHL-1 was conducted during the COVID-19 pandemic, which affected clinical and safety outcomes. To account for this, deaths considered COVID-19-related were censored from survival analyses. However, there is uncertainty regarding the appropriateness of this adjustment and the robustness of the resulting analyses, used in the economic base case. The company argues that the dose optimisation cohort, recruited largely after the peak of the pandemic, is more representative of current Scottish practice and that outcomes from this cohort closely align with the COVID-modified expansion data. However, baseline characteristics differed between the expansion and optimisation cohorts, with the latter exhibiting more favourable prognostic features including fewer prior lines of therapy. These differences may have partly contributed

to the observed differences in survival outcomes between the COVID-unmodified expansion and optimisation cohorts.

- Some factors may limit the generalisability of the study results. Study enrolment required documented CD20-positive mature B-cell neoplasms; however, CD20 expression was not re-confirmed at screening. Exploratory analyses suggest poorer outcomes in patients with a shorter interval since last anti-CD20 therapy, those refractory to their most recent anti-CD20–containing regimen and those with low CD20 expression, introducing uncertainty about the benefit in these subgroups. However, these analyses were exploratory and based on small patient numbers, and should therefore be interpreted with caution. [2]

*Other data were also assessed but remain confidential.**

4.3. EMA conditional marketing authorisation specific obligations

As part of the specific obligations outlined by the European Medicines Agency (EMA), the marketing authorisation holder should submit the final clinical study report for the key EPCORE NHL-1 indolent NHL expansion cohort study by Q2 2028 and FL optimisation cohort by Q3 2029. In addition, the marketing authorisation holder should submit results by Q4 2030 for the ongoing, phase III M20-638 study, which compares epcoritamab in combination with lenalidomide and rituximab, with lenalidomide and rituximab in subjects with R/R FL after at least one prior anti-CD20 containing chemoimmunotherapy regimen. [2]

The EMA specific obligations are unlikely to address the key uncertainties in the clinical evidence presented as no comparative data on the use of epcoritamab as monotherapy in the licensed indication will be generated.

4.4. Clinical expert input

Clinical experts consulted by SMC generally considered that epcoritamab fills an unmet need in this therapeutic area, namely as there are very limited treatment options in the third line plus setting. They considered that it is a therapeutic advancement, given the promising response rates observed.

4.5. Service implications

Clinical experts consulted by SMC generally considered that the introduction of this medicine may impact patient care and service delivery, mainly due to the need for frequent dosing, monitoring associated with bispecific antibodies, and the continuous nature of treatment. However, some experts noted that services already have established pathways from use in Diffuse Large B-Cell Lymphoma, and the number of eligible patients is expected to be small.

5. Patient and clinician engagement (PACE)

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of epcoritamab, as an orphan-equivalent medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- Follicular lymphoma (FL) is a chronic, essentially incurable, and typically slow-growing cancer that can impose a substantial long-term burden. FL can cause debilitating symptoms, particularly fatigue, weight loss, fevers, night sweats, recurrent infections, and reduced physical functioning. While some patients experience prolonged periods with few symptoms, others face recurrent relapses, shorter remissions, and reduced treatment effectiveness over time. Relapsed or refractory FL can have significant psychological, social, and economic impacts. Symptoms may limit patients' ability to work and participate in usual activities. Uncertainty about future relapses and treatment outcomes can lead to anxiety for patients and their families.
- Patients with multiple relapsed or refractory disease are an area of considerable unmet need. Several treatment options are available for relapsed or refractory FL; however, there is no established standard of care, and treatment choice is influenced by factors such as prior therapies and duration of remission and co-morbidities. Outcomes generally worsen with successive relapses, leading to shorter remissions, increasing treatment resistance and poorer outcomes.
- With its novel mechanism of action, epcoritamab offers an important additional chemotherapy-free treatment for patients with relapsed or refractory FL who have limited remaining treatment options. It has an acceptable toxicity profile and is generally well tolerated, especially when compared with the side effects of repeated courses of chemotherapy. By improving disease control, epcoritamab may help alleviate lymphoma-related symptoms and support patients in maintaining their daily activities, independence and quality of life.
- Epcoritamab is administered by subcutaneous injection, unlike most existing treatments that require prolonged intravenous infusions. It can be delivered in the outpatient setting. This may reduce the burden of prolonged hospital attendance, minimise disruption to work, family and social activities and address the need for less burdensome treatment approaches.
- For families and carers, epcoritamab may help reduce the practical and emotional impact of living with relapsed or refractory FL and may help alleviate concerns about increasingly limited treatment options as the disease progresses.
- Treatment delivery will require appropriate infrastructure and trained staff for the administration and monitoring of epcoritamab, including the management of cytokine release syndrome and neurological toxicities. PACE clinicians highlighted that many haematology centres are already familiar with epcoritamab through its use in other indications.

Additional Patient and Carer Involvement

We received a patient group submission from Lymphoma Action which is a registered charity. Lymphoma Action has received 7.2% pharmaceutical company funding in the past two years, including from the submitting company. A representative from Lymphoma Action participated in the PACE meeting. The key points of their submission have been included in the full PACE statement considered by SMC.

6. Summary of Comparative Health Economic Evidence

6.1. Economic case

Table 6.1 describes the economic case.

Table 6.1 Description of economic analysis

Criteria	Overview
Analysis type	Cost-utility analysis
Time horizon	Lifetime horizon - 35.2 years with a mean starting age of 64.8 years
Population	Adult patients with R/R FL after two or more lines of systemic therapy.
Comparators	Basket comparator representing current ≥3L care, including rituximab-based chemotherapy, chemotherapy, rituximab plus lenalidomide (R^2), and obinutuzumab plus bendamustine. Comparator proportions were informed by HMRN data.[10]
Model description	Partitioned survival model including progression-free, progressed disease, and death states. Cycle length was 1 week.
Clinical data	Epcoritamab efficacy was sourced from the EPCORE NHL-1 study[7] using MAIC-reweighted and COVID-adjusted OS, PFS and time on treatment (TTD) data from the dose expansion cohort. Relative efficacy between epcoritamab and the basket comparator was estimated from an unanchored MAIC (described in Section 2.4). Comparator TTD data were informed from the same source used in the MAIC, the HMRN dataset. AE rates for epcoritamab were sourced from EPCORE NHL-1. Comparator AE rates were estimated using a weighted approach based on AE rates from individual therapies within the comparator basket, weighted according to expected treatment use.
Extrapolation	OS and PFS for the epcoritamab arm were extrapolated using log-normal distributions. The hazard ratios derived from the MAIC were applied to the extrapolated epcoritamab OS and PFS curves to estimate survival for the comparator basket. TTD was modelled independently by arm using a log-normal distribution for epcoritamab arm and a log-logistic curve for the comparator arm. A maximum duration of 3 years was applied for complete responders receiving epcoritamab.
Quality of life	Utility values were informed by EQ-5D-3L data collected in EPCORE NHL-1. Progression free utility values were derived directly from study data. Progressed disease utility values estimated from participants of the EPCORE NHL-1 study lacked face validity, being too similar to the progression free values. Instead the submitting company applied the difference in progression free utility and progressed disease utility from a secondary source as a decrement to progression free utility values estimated from EPCORE NHL-1.[12] AE disutilities were not included, having been assumed to be included in the health state utility values.
Costs and resource use	Included medicine acquisition, administration, disease management, monitoring, AEs, subsequent treatment, end-of-life care, and healthcare resource use.
PAS	A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a discount was offered on the list price. A PAS discount is in place for obinutuzumab, and contract price agreements were in place for chlorambucil, rituximab, bendamustine, and lenalidomide. These were included in the results used for decision-making.

6.2. Results

SMC considered results for decision-making that took into account all relevant PAS and contract prices agreements. SMC is unable to present these results due to competition law issues.

Table 6.2: Base case analysis Epcoritamab vs Current 3L+ Care

	Total Costs (£)	Total QALYs	Incr. Costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Epcoritamab	CIC	6.079	CIC	9.448	4.269	CIC
Current ≥3L care	CIC	1.810	-	-	-	-

Costs and QALYs discounted; LYs undiscounted.

Abbreviations: CIC, commercial in confidence; ICER, incremental cost-effectiveness ratio; LYG, life year gained; QALYs, quality-adjusted life years.

The quality-adjusted life year (QALY) gain was primarily driven by a substantial increase in time spent in the progression-free health state for epcoritamab compared with the comparator. There was also a notable increase in the QALYs accrued in the progressed disease health state due to an improved OS benefit.

The key cost drivers came from the higher acquisition costs for epcoritamab compared with the comparator, as well as higher disease management costs. The higher disease management costs in the epcoritamab arm were driven by longer time spent in both health states (due to the improved PFS and OS).

*Other data were also assessed but remain confidential.**

6.3. Sensitivity analyses

A range of sensitivity and scenario analyses were considered and descriptions of these key scenarios are provided in Table 6.3.

Table 6.3: Summary of scenario analyses

#	Parameter	Base case assumption	Scenario	Incr. Costs (£)	Inc. QALYs	ICER (£/QALY)
-	***Base case***			CIC	4.269	CIC
1a			5-year maximum treatment duration	CIC	4.269	CIC
1b			Maximum treatment duration excluded	CIC	4.269	CIC
2	Utility values	EPCORE NHL-1 with Wild et al. PD adjustment	Cognet et al.[13]	CIC	3.685	CIC
3	Comparator market shares	Composition of current 3L+ care treatment basket - HMRN	Composition of current 3L+ care treatment basket -TA894	CIC	4.269	CIC
4a	Patient Population	COVID-modified survival	COVID-unmodified survival	CIC	2.358	CIC
4b			Omicron-adjusted	CIC	3.764	CIC
4c			IPCW - adjusted	CIC	4.255	CIC

5a	Epcoritamab PFS distribution	Log-normal	Exponential	CIC	3.976	CIC
5b			Gamma	CIC	4.108	CIC
5c			Generalised gamma	CIC	4.461	CIC
6a	Epcoritamab OS distributions	Log-normal	Generalised gamma	CIC	2.868	CIC
6b			Exponential	CIC	3.223	CIC
6c			Log-logistic	CIC	3.964	CIC
6d			Gamma	CIC	3.564	CIC
7a	Epcoritamab TTD distributions	Log-normal	Weibull	CIC	4.269	CIC
7b			Used KM data up to 42.11 months	CIC	4.269	CIC
8	Comparator TTD distributions	Log-logistic	Exponential	CIC	4.269	CIC
9	Time horizon	Lifetime horizon	10-years	CIC	2.511	CIC
10a	Combined scenarios	1b & 6a		CIC	2.868	CIC
10b		5a & 6a		CIC	2.626	CIC
11a		4a, 5a, 6a		CIC	1.515	CIC
11b		2c, 4a, 5a, & 6a		CIC	1.315	CIC
11c		2c & 4a		CIC	2.042	CIC

Abbreviations: CIC, commercial in confidence; HMRN, Haematological Malignancy Research Network; Incr, incremental; ICER, incremental cost-effectiveness ratio; KM, Kaplan-Meier; NHL, non-Hodgkin lymphoma; PFS, progression-free survival; PD, progressed disease; OS, overall survival; TTD, time to treatment discontinuation.

6.4. Key strengths

- The company used a partitioned survival model, which was an appropriate approach for this indication.
- The economic model included relevant cost categories expected for this indication, with inputs generally sourced from relevant UK/NHS references.

6.5. Key uncertainties

- Clinical effectiveness was informed by a single-arm, open-label study, with data remaining immature, particularly for OS, due to limited follow-up and few observed events. In the absence of direct comparative data, relative effectiveness estimates were informed by an unanchored MAIC, which was associated with considerable uncertainty. One-way sensitivity analyses identified the MAIC-derived OS hazard ratio as a key influential parameter within the model, however the impact of alternative assumptions regarding comparator effectiveness could not be explored fully in scenario analyses.
- The base case relied on COVID-19 modified survival analyses from EPCORE NHL-1, which the submitting company stated better represented expected outcomes outside of the pandemic period in which the central study was run. The Committee considered the appropriateness of these adjustments to be uncertain. Scenario analyses using unmodified survival data resulted in increases in the incremental cost-effectiveness ratio (ICER) (see Scenario 4a, Table 6.3), indicating that the cost-effectiveness results were sensitive to the handling of COVID-related events. However, alternative COVID-19 adjustments methods (Scenario 4b and 4c) produced broadly similar ICERs to the base case.

- There was inherent uncertainty in the OS and PFS extrapolations due to the immaturity of the EPCORE NHL-1 data, particularly for OS. As a result, long-term survival estimates were heavily dependent on the choice of parametric distributions, with substantial divergence between alternative extrapolated curves beyond the observed study period. More conservative OS extrapolations resulted in increases in the ICER (Scenarios 6a, 6b & 6d), demonstrating that the economic results were sensitive to long-term survival assumptions.
- The company assumed that patients achieving a complete response discontinued epcoritamab after a maximum treatment duration of 3 years, based on clinical opinion. This assumption influenced the cost-effectiveness results by limiting treatment costs while patients continue to accrue health benefits. While long-term evidence to support this assumption was limited, it was considered to be a plausible approach. Scenario analyses removing the stopping rule resulted in an increase in the ICER (Scenario 1b), indicating that the cost-effectiveness results are sensitive to the assumed treatment duration.

7. Conclusion

The Committee considered the benefits of epcoritamab in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that as epcoritamab is an orphan equivalent medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and the output from the PACE process, the Committee accepted epcoritamab for use in NHSScotland.

8. Guidelines and Protocols

The Scottish Consensus Clinical Management Guideline for Follicular Non-Hodgkin Lymphoma was updated in 2024.[14]

The British Society for Haematology published guidelines for the management of follicular lymphoma in 2020. [4]

The European Society for Medical Oncology (ESMO) published guidelines for the management of follicular lymphoma in 2021[3], with updated guidelines provided in 2026.[15]

The National Institute for Health and Care Excellence (NICE) published guidelines for the management of follicular lymphoma in July 2016.[16]

9. Additional Information

9.1. Product availability date

19 June 2025

Table 9.1 List price of medicine under review

Medicine	Dose regimen	Cost per cycle (£)
epcoritamab	**0.16 mg priming dose on day 1, 0.8 mg intermediate dose on day 8, 3 mg intermediate dose on day 15, and 48 mg full dose on day 22 of cycle 1 and thereafter (weekly during cycles 2 to 3, every 2 weeks during cycles 4 to 9 and every 4 weeks during cycle 10 and beyond), until disease progression or unacceptable toxicity.**	**Cycle 1: £8,210 Cycles 2 to 3: £26,272 Cycles 4 to 9: £13,136 Cycle 10 onwards: £6,568**

Costs from BNF online on 01 May 2026. Costs calculated using the full cost of vials assuming wastage. Costs do not take any patient access schemes into consideration.

10. Company Estimate of Eligible Population and Estimated Budget Impact

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS.

This template does not incorporate any PAS discounts associated with comparator medicines or PAS associated with medicines used in a combination regimen.

*Other data were also assessed but remain confidential.**

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This assessment is based on data submitted by the applicant company up to and including 12 June 2026.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC includes Scottish national contract prices in its decision-making. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document.

Patient Access Schemes (PAS): A PAS is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. The Patient Access Scheme Assessment Group (PASAG), established under the auspices of Public Services Delivery Scotland, reviews and advises NHS Scotland on the feasibility and acceptability on implementing proposed schemes. PASAG operates separately from SMC to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHS Scotland on the basis of a PAS that has been considered acceptable for implementation by PASAG, a set of guidance notes on the operation of the scheme will be circulated to health boards' Area Drugs and Therapeutics Committees prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.