

Single Technology Appraisal

Epcoritamab for treating relapsed or refractory follicular lymphoma after 2 or more systemic treatments [ID6338]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Epcoritamab for treating relapsed or refractory follicular lymphoma after 2 or more systemic treatments [ID6338]

Contents:

The following documents are made available to stakeholders:

Access the [final scope and final stakeholder list](#) on the NICE website.

- 1. Company submission from AbbVie:**
 - a. Full submission
 - b. Summary of Information for Patients (SIP)
- 2. Clarification questions and company responses**
- 3. Patient group, professional group, and NHS organisation submissions from:**
 - a. Follicular Lymphoma Foundation
 - b. Lymphoma Action
- 4. Expert personal perspectives from:**
 - a. Dr Kim Linton – Clinical expert, nominated by AbbVie
 - b. Dr Mark Bishton – Clinical expert, nominated by British Society for Haematology
 - c. Mr Andy Brown – Patient expert, nominated by Lymphoma Action
- 5. External Assessment Report** prepared by Birmingham Centre for Evidence and Implementation Science (BCEIS)
- 6. External Assessment Report – factual accuracy check**
 - a. External Assessment Report – factual accuracy check
 - b. Factual accuracy check addendum

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Epcoritamab for treating relapsed or refractory follicular lymphoma patients after three or more systemic treatments [ID6338]

Company evidence submission

28th April 2025

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Abbreviations

ACST	Autologous Stem Cell Transplantation
ADA	Anti-Drug Antibodies
AE	Adverse Events
AESIs	Adverse Events of Special Interest
AIC	Akaike Information Criterion
ALT	Alanine Transaminase
aNHL	Aggressive Non-Hodgkin Lymphoma
ASCO	American Society of Clinical Oncology
ASH	American Society of Haematology
AST	Aspartate Transaminase
BIC	Bayesian Information Criterion
BMI	Body Mass Index
BOR	Best Overall Response
BSA	Body Surface Area
CAR-T	Chimeric Antigen Receptor T-cell
CEM	Cost-Effectiveness Model
CEAC	Cost-Effectiveness Acceptability Curve
CI	Confidence Interval
CIT	Chemoimmunotherapy
CLL	Chronic Lymphocytic Leukaemia
CR	Complete Response
CRS	Cytokine Release Syndrome
CSR	Clinical Studies Report
CT	Computer Tomography
CTLS	Clinical Tumour Lysis Syndrome
DLBCL	Diffuse Large B-cell Lymphoma
DoCR	Duration of Complete Response
DOR	Duration Of Response
DS	Deauville Score
ECOG	Eastern Cooperative Oncology Group
EHA	European Hematology Society
EMA	European Medicines Agency
ESMO	European Society for Medical Oncology
FACT-LymS	Functional Assessment of Cancer Therapy
FAS	Full Analysis Set
FDG	Fluorodeoxyglucose

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FL	Follicular Lymphoma
FLIPI	Follicular Lymphoma International Prognostic Index
GELF	Groupe d'Etude des Lymphomes Folliculaires
HGBCL	High Grade B-cell Lymphoma
HMRN	Haematological Malignancy Research Network
HR	Hazard Ratio
HRQoL	Health Related Quality of Life
HSCT	Hematopoietic Stem Cell Transplantation
IAS	Immunogenicity Analysis Set
ICANS	Immune Effector Cell-Associated Neurotoxicity Syndrome
ICER	Incremental Cost-Effectiveness Ratio
ICML	International Conference of Malignant Lymphoma
iNHL	Indolent Non-Hodgkin Lymphoma
IR	Intermediate Response
IRC	Independent Review Committee
IRST	Involved Site Radiotherapy
IV	Intravenous
KM	Kaplan-Meier
LDH	Lactate Dehydrogenase
LEO	Lymphoma Epidemiology of Outcomes
LMM	Linear Mixed Models
LOT	Line Of Treatment
LY	Life Year
LYRIC	Lymphoma Response to Immunomodulatory Therapy Criteria
MAIC	Matching-Adjusted Indirect Comparison
MEDLINE	Medical Literature Analysis and Retrieval System
mFAS	Modified Full Analysis Set
MRD	Minimum Residual Disease
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
MZL	Marginal Zone Lymphoma
NCI	National Cancer Institute
NHL	Non-Hodgkin Lymphoma
NHS	National Health Service
NICE	National Institute of Health and Care Excellence
NR	Not Reported
OB	Obinutuzumab with Bendamustine
ONS	Office of National Statistics

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ORR	Overall Response Rate
OS	Overall Survival
PAS	Patient Access Scheme
PD	Progressive Disease
PET	Positron Emission Tomography
PFS	Progression Free Survival
PHA	Proportional Hazard Assumptions
PK	Pharmacokinetic
PMBCL	Primary Mediastinal B-cell Lymphoma
POD24	Disease progression within 24 months
PP	Per Protocol
PRR	Partial Response Rate
PSS	Personal Social Services
QALY	Quality-Adjusted Life Years
R/R	Relapse/ Refractory
PSM	Partitioned Survival Model
R ²	Rituximab and Lenalidomide
R-CHOP	Rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone
RES	Response Evaluable Set
RP2D	Recommended Phase 2 Dose
RWE	Real-World Evidence
SAF	Safety Analysis Set
SC	Subcutaneous
SD	Standard Deviation
SE	Standard Error
SLL	Small lymphocytic Lymphoma
SLR	Systematic Literature Review
SPD	Sum of Product of Diameters
TEAEs	Treatment Emergent Adverse Events
TTNT	Time To Next Treatment
TTR	Time To Response
ULN	Upper Limit of Normal
VAS	Visual Analogue Scale
WHO	World Health Organisation

Executive Summary

Follicular lymphoma

- Follicular lymphoma (FL) arises from mature B-cells, and is the most common subtype of indolent lymphoma, accounting for 70% of low-grade non-Hodgkin lymphomas.¹
- About 2,330 people are diagnosed with FL every year in the UK. FL can develop at any age, but is most common in people over 60 years of age.¹
- There are few effective treatment options for individuals with FL, and relapses are common. Treatment options are usually exhausted within two or three lines of therapy,² with just over a third of patients progressing to 4L+ treatment from 3L+.³ At this stage, current strategies often involve recycling ineffective treatments, leading to poor outcomes.⁴
- 4L+ FL is an end-of-life disease. Most patients do not survive longer than a year (median [REDACTED]) and generally experience rapid disease progression within several months (median [REDACTED]).⁵
- Despite this, there are currently no NICE-recommended treatments specifically at 3L+ FL or beyond and there have been no NICE-recommended treatments in FL since 2020.
- Current treatments are mostly delivered intravenously and are associated with debilitating side effects,⁶ placing a high burden on already heavily pre-treated and immunosuppressed patients.
- Additionally, patients currently spend an average of [REDACTED] each year (on an annualised basis) in inpatient settings with overnight stays due to 4L+ FL treatment administration, monitoring, and disease.⁵
- As such, there is a high unmet need for a tolerable and effective alternative treatment that can lead to durable disease control and help relieve patients and the health system of the burden with current care in 4L+ FL.

Epcoritamab

- Epcoritamab is an innovative targeted therapy offering an alternative to current anti-CD20 and/or chemotherapy-based regimens. It is a bispecific antibody that has demonstrated clinically significant overall survival benefits as well as deep and durable responses in both diffuse large B-cell lymphoma (DLBCL) and FL.
- Epcoritamab is administered subcutaneously, enabling quick and flexible administration and potentially reducing patient, carer, and health system burden.

Clinical outcomes with epcoritamab in 4L+ FL

- The population considered in the submission (4L+ FL) is narrower than the anticipated marketing authorisation (3L+ FL) for epcoritamab, reflecting the area of highest unmet need in NHS clinical practice.⁷
- The heavily pre-treated single-arm EPCORE-NHL1 trial showed **durable overall survival (OS) with epcoritamab in 4L+ FL. The median OS was**

██████ over a median of █████ months follow-up. The median PFS was reached at █████ months.⁷

- **Over half of patients achieved deep and meaningful responses with epcoritamab. In 4L+ FL, █████% achieved a complete response (CR) and a total of █████% achieved an overall response (OR).**⁷
- Epcoritamab demonstrated a tolerable safety profile. All treatment-emergent adverse events (TEAEs) were manageable and did not adversely impact patient quality of life (QoL). Patients reported a stable QoL with epcoritamab throughout follow-up.⁷

Indirect treatment comparison

- Current care in England, comprising of a “basket” of different chemoimmunotherapy (CIT) and chemotherapy treatments, was identified as the main comparator for epcoritamab in 4L+ FL and was sourced from the Haematological Malignancy Research Network (HMRN).⁵
- An unanchored matching-adjusted indirect treatment comparison (MAIC) showed that epcoritamab reduces the risk of death by █████ compared with current 4L+ care (█████). Treatment with epcoritamab also significantly reduced the risk of progression or death (PFS) by █████ compared with current 4L+ care (█████).
- Sustained survival benefits for epcoritamab vs. current 4L+ care were driven by deep responses. Population-adjusted results from the MAIC showed that patients treated with epcoritamab were more likely to achieve a CR and OR compared with patients treated with current 4L+ care:
 - CR: █████ for epcoritamab vs. █████ with current 4L+ care (█████)
 - OR: █████ for epcoritamab vs. █████ with current 4L+ care (█████)

Cost effectiveness

- FL in the 4L+ setting is an end-of-life disease. Given the high mortality rate and poor QoL with existing care in England, this appraisal meets the criteria for NICE’s severity weighting of ×1.2 (proportional QALY shortfall of 90.93%).
- A cost-utility analysis using a partitioned survival model (PSM) showed that epcoritamab is a cost-effective use of NHS resources in 4L+ FL. The resulting ICER for epcoritamab compared with current 4L+ care is £█████ after applying the severity modifier and the current PAS price for epcoritamab (not including any commercial discounts for comparator medicines).⁸
- Scenario and sensitivity analyses show stability in model results and the limited impact of any residual uncertainty.

Summary

Epcoritamab could be a life-changing treatment for patients with 4L+ FL, who currently face limited options and a life expectancy of under a year.⁵ It has the potential to transform the management of FL through a new mechanism of action (MoA) when patients have exhausted other options at earlier lines. Epcoritamab is a chemotherapy-free regimen that is delivered subcutaneously and is expected to be more convenient for patients, carers and the health care system compared with existing intravenous and chemotherapy-based regimens.

Company evidence submission for epcoritamab for treating relapsed or refractory follicular lymphoma patients after three or more systemic treatments

1 Decision problem, description of the technology and clinical care pathway

1.1 Decision problem

This submission focuses on a narrower population than the technology’s marketing authorisation.

Anticipated MA wording	
This Submission	Epcoritamab, as monotherapy, for the treatment of adult patients with relapsed or refractory FL after three or more lines of systemic therapy

There is a significant unmet need for patients with relapsed or refractory follicular lymphoma receiving their fourth or later line of therapy (4L+). During UK clinical expert interviews conducted by AbbVie, NHS Consultant haematologists noted that there are limited treatment options for 4L+ patients, and that there is a desperate need for innovative therapies for patients who relapse or become refractory to existing treatments.⁹ These 4L+ patients have notably poor survival outcomes: real-world data from the UK showed that median overall survival among patients with ≥3 prior treatments was less than a year (■ months) while median progression-free survival was just ■ months.⁵

The decision problem addressed in this submission is presented in Table 1.

Table 1. Decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with relapsed or refractory follicular lymphoma after 2 or more systemic treatments	Adults with relapsed or refractory follicular lymphoma after 3 or more systemic treatments	The company submission focuses on the patient population with the greatest clinical unmet need and where there are limited treatment options.
Intervention	Epcoritamab	Epcoritamab	N/A
Comparator(s)	Established clinical management without epcoritamab. Treatment choice will depend on previous treatments, and how effective those treatments were. • Lenalidomide with rituximab • Obinutuzumab with bendamustine followed by obinutuzumab maintenance • Rituximab monotherapy • Rituximab with chemotherapy • Best supportive care	The comparators considered in this submission: • Current 4L+ care as a basket of rituximab-based chemotherapy, chemotherapy, lenalidomide with rituximab, and other immune-based regimens	Based on consultation with UK clinical experts, the consensus is that there is no standard of care for relapsed/refractory FL 4L+. ⁹ Treatment is individualised. Therefore, the comparator treatment basket considered within this submission aligns with and reflects the lack of any specific standard of care treatment for patients in current UK clinical practice.
Outcomes	The outcome measures to be considered include: • Overall survival • Progression-free survival • Response rates • Adverse effects of treatment • Health-related quality of life.	The outcomes measure to be considered include: • Overall survival • Progression-free survival • Response rates (ORR, CR, PR) • Adverse effects of treatment • Time to treatment discontinuation • Health-related quality of life	All outcomes requested in the final scope are presented, with additional outcomes reported that are important to demonstrate the benefits of epcoritamab.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year.	As per NICE scope	N/A

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	The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability and cost of biosimilar and generic products should be taken into account.		

ORR, overall response rate; CR, complete response; FL, follicular lymphoma; PR, partial response; R/R, relapse/refractory

1.2 Description of the technology being evaluated

A summary of the mechanism of action, marketing authorisation status, cost and administration requirements associated with epcoritamab are presented in Table 2. The draft summary of product characteristics is provided in Appendix A.

Table 2. Technology being evaluated

UK approved name and brand name	Epcoritamab (Tepkinly®)
Mechanism of action	Epcoritamab is an IgG1-bispecific antibody engineered to bind to CD3 on the surface of T-cells and CD20 on malignant B-cells to promote T-cell mediated cell death. ¹⁰ The activity of epcoritamab is dependent on the simultaneous engagement of CD20-expressing cancer cells and CD3-expressing T-cells, ¹⁰ a mechanism that differs from conventional CD20 targeting monoclonal antibodies that introduce cytotoxicity through Fc-mediated effector functions.
Marketing authorisation/CE mark status	Epcoritamab has marketing authorisation in the United Kingdom for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy. In the European Union, after epcoritamab was licensed, a new indication application (for the treatment of adult patients with relapsed or refractory follicular lymphoma after two or more lines of systemic therapy) was approved on 16 August 2024. In the UK, an application for a new indication (for follicular lymphoma) was submitted to the MHRA via the international recognition procedure (reference regulator: EMA) on [REDACTED] and a decision is expected in [REDACTED]
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Epcoritamab, as a monotherapy, is indicated for the [REDACTED]. This submission covers a subpopulation of this indication: patients diagnosed with relapsed, progressive or refractory follicular lymphoma that have undergone three or more prior lines of treatment. Contraindications for epcoritamab include hypersensitivity to epcoritamab or any of the following excipients: • Sodium acetate trihydrate • Acetic acid • Sorbitol • Polysorbate 80 • Water for injections Women of childbearing potential should be advised to use effective contraception during treatment with epcoritamab and for at least 4 months after the last dose. Epcoritamab is not recommended during pregnancy and in women of childbearing potential not using contraception. Verify pregnancy status in females of reproductive potential prior to initiating epcoritamab treatment.

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Method of administration and dosage	Epcoritamab is for subcutaneous injection only, preferably in the lower part of the abdomen or the thigh and should be administered by a healthcare professional qualified in the use of anti-cancer therapies (see Table 3 below). Table 3. Dosing regimen for epcoritamab <table><tr><th>Cycle</th><th colspan="4">1</th><th colspan="4">2 and 3</th><th colspan="2">4 to 9</th><th>10+</th></tr><tr><th>Day of Cycle</th><td>1</td><td>8</td><td>15</td><td>22</td><td>1</td><td>8</td><td>15</td><td>22</td><td>1</td><td>15</td><td>1</td></tr><tr><th>Dose (mg)^a</th><td>0.16</td><td>0.8</td><td>3</td><td>48</td><td>48</td><td>48</td><td>48</td><td>48</td><td>48</td><td>48</td><td>48</td></tr></table> ^a 0.16 mg is step-up dose 1, 0.8 mg is step-up dose 2, 3 mg is step-up dose 3 and 48 mg the full dose.	Cycle	1				2 and 3				4 to 9		10+	Day of Cycle	1	8	15	22	1	8	15	22	1	15	1	Dose (mg) ^a	0.16	0.8	3	48	48	48	48	48	48	48	48
Cycle	1				2 and 3				4 to 9		10+																										
Day of Cycle	1	8	15	22	1	8	15	22	1	15	1																										
Dose (mg) ^a	0.16	0.8	3	48	48	48	48	48	48	48	48																										
Additional tests or investigations	No additional testing or investigations are required to determine eligibility for epcoritamab use in NHS clinical practice.																																				
List price and average cost of a course of treatment	Confirmed list price of epcoritamab: 4mg/0.8ml concentrate for solution for injection vials (pack of 1) = £547.33 48mg/0.8ml solution for injection vials (pack of 1) = £6,568.00 When considering the patient access scheme (PAS) discount for epcoritamab, the annual cost of a course of treatment with epcoritamab is [REDACTED] in year 1 and [REDACTED] in each year thereafter. At list price, the annual cost of a course of treatment with epcoritamab is £166,076.56 in year 1 and £85,618.57 in each year thereafter.																																				
Patient access scheme (if applicable)	A simple PAS is in place for epcoritamab. The epcoritamab price with the PAS applied is [REDACTED].																																				

Abbreviations: EMA, emergency medicines agency; NHS, National Health Service; PAS, patient access scheme

1.3 Health condition and position of the technology in the treatment pathway

Relapsed and refractory follicular lymphoma:

- Follicular lymphoma (FL) arises from mature B-cells in germinal centres and is the most common subtype of indolent lymphoma, accounting for 35% of non-Hodgkin lymphomas (NHLs) and 70% of indolent NHLs (iNHL). Approximately, 2,330 new FL patients are diagnosed each year in the UK.⁵
- FL patients are at high risk of relapse (lymphoma returning after successful treatment)¹¹ or refractory disease (lymphoma that doesn't respond to treatment), with FL becoming increasingly refractory to treatment and more likely to relapse sooner after each line of therapy.¹² Consequently, overall and progression free survival (OS and PFS) decrease significantly after first relapse and with each subsequent relapse.^{3,13}
- In a UK real world analysis, patients with R/R FL receiving 4L+ therapy had low response rates to current treatment options, with only █% of patients achieving a complete response.⁵ In this context, median OS was █ months and median PFS was just █ months.⁵
- Patients with R/R FL have a poor quality of life, experiencing a range of debilitating symptoms including weight loss, fatigue and difficulties walking or swallowing due to swollen lymph nodes.¹⁴ With FL being considered an incurable, chronic disease, patients experience anxiety and depression associated with the uncertainty about relapse.¹⁵

Current treatment pathways

- Multiple-relapsed FL is a life-limiting disease, with treatment aiming to control symptoms and achieve remission. There are no standardised treatment pathways for patients with follicular lymphoma, with limited treatment options available at 4L+.
- In many cases, once a patient reaches 4L+ treatment, the only treatment option available is the recycling of previously unsuccessful therapies. Approximately, two thirds of patients who receive third-line treatment will progress to 4L treatment where there is no alternative than to rechallenge with toxic and poorly efficacious chemotherapy containing regimens.³ Retreatment with multiple rounds of chemoimmunotherapy has a detrimental impact on patient HRQoL that is not wholly captured in QALY outcomes (both physical and psychological).¹⁶
- The lack of new treatment options that allow for deep responses to be achieved has been raised as a concern by patient advocacy groups in multiple previous NICE appraisals.¹⁶⁻¹⁹
- Current treatment options are predominantly administered via IV infusion, resulting in hospital stays and patient monitoring periods, putting pressure on patients, carers and the healthcare system alike. Patients in 4L+ FL currently

spend an average of [REDACTED] each year (on an annualised basis) in inpatient settings with overnight stays.⁵

Epcoritamab

- Epcoritamab is a novel, humanised IgG1-bispecific antibody that binds the B-cell antigen CD20 and T-cell antigen CD3.
- Although the marketing authorisation for epcoritamab is expected to include [REDACTED], AbbVie are seeking reimbursement in patients who have received three or more lines of prior therapy as these patients have the highest unmet need, i.e. poorest survival outcomes and most limited access to effective treatments.
- If recommended, epcoritamab will be the only subcutaneously administered bispecific monoclonal antibody offering quicker and more convenient administration compared with IV chemotherapy, therefore, alleviating pressure on healthcare systems.
- Epcoritamab is a chemotherapy-free regimen that maintains patient QoL without the chemo-specific toxicities such as cardiac risk, severe neutropenia and alopecia.²⁰

In summary, epcoritamab is a novel and alternative treatment for patients with R/R patients at 4L+, offering a tolerable, conveniently administered, effective treatment and durable disease control.

1.3.1 Disease Background

B-cell development is a vital part of the immune system and results in the production of highly specific antibodies.²¹ The development of B-cells is a complex process, regulated by a series of checkpoints.²² It begins with immature B-cells in the bone marrow and progresses to mature B-cells at secondary maturation sites (the spleen and germinal centres).²³ The expression of CD20, a cell surface protein, is a key marker of mature B-cells.²⁴ Aberrant B-cell development can give rise to a range of different cancers.²⁵ Cancers arising from immature cells in the bone marrow are known as leukaemias, whilst those arising from mature B-cells are known as lymphomas. CD20 is expressed on the surface of FL cancer cells, which can be therapeutically targeted by bispecific antibodies such as epcoritamab.²⁶

1.3.2 Follicular Lymphoma

Lymphomas are broadly categorised into two subgroups, Hodgkin and Non-Hodgkin lymphoma (NHL). The NHL category covers a wide range of lymphomas, including but not limited to mantle cell lymphoma (MCL), follicular lymphoma (FL) and DLBCL. FL arises from mature B-cells in germinal centres. FL is the most common form of iNHL and is often considered an indolent (slow growing) cancer, with the exception of grade 3B that follows a more aggressive clinical course. Patients are at a high risk of relapse (cancer returning after treatment) or refractory disease (a lymphoma that stops responding to treatment).³ By the 4L+ stage, R/R FL is no longer considered an indolent disease and is more akin to an end of life disease, with limited treatment options.

1.3.3 Burden of FL

Individuals with FL present with B symptoms (a series of symptoms associated with NHLs), including drenching sweats, often at night, intermittent fevers, and unexplainable weight loss. Other symptoms include swelling of lymph nodes, which may be visible in the neck, armpit or groin and fatigue. Currently, there is no cure for FL and it is considered a chronic, life-limiting disease, with treatments aiming to get patients into remission, where their symptom burden is greatly reduced.²⁷ Most patients presenting with advanced stage disease experience recurrent relapses requiring multiple lines of

therapy to achieve remission. By their 4L+ of therapy, patients' life expectancy is typically less than one year.⁵

Studies investigating health-related quality of life (HRQoL) show significantly reduced HRQoL among patients with FL compared with the general UK population.²⁸ Studies have also shown that following a FL diagnosis, many individuals are unable to continue work, with this becoming increasingly true in those receiving systemic therapy.²⁹ Additionally, patients diagnosed with iNHL have lower emotional well-being than those without.^{30,31}

AbbVie recently carried out a study to understand the patient experience of living with FL, which involved asking 15 clinicians and 13 patients or carers from the UK, Germany and Japan about their experiences during 60 minutes interviews.³² Patients with later stage FL, who were on their second or later lines of treatment, reported feeling disappointed, exhausted and dismayed that they needed to restart treatment. Further, patients with follicular lymphoma reported experiencing shock at their diagnosis and that they lived with high levels of anxiety over the fear of the disease returning.³²

Disease relapse has a further significant impact on a patient's HRQoL with individuals being more likely to report higher levels of depression or anxiety than those in remission.²⁸ For those with incurable lymphomas, the fear of progression or relapse is also commonly reported and greatly contributes to the debilitating symptomology of the condition, especially in those who reach later lines of treatment where new therapeutic options are limited.¹⁵ Median progression free survival is only [REDACTED] at 4L+ with the currently available treatments.⁵ This is compounded by the fact that in FL, survival outcomes decrease with each line of therapy due to increasing chemo-refractoriness, an issue particularly pertinent to those who require 4L+ treatment, the target population of this appraisal.^{33,34}

While there is limited available information pertaining to the impact of a FL diagnosis on caregivers, a report looking at lymphoma and chronic lymphocytic leukaemia (CLL) in general found that 75% of caregivers, family or friends reported that treatment wait times had a moderate to severe effect on their wellbeing.¹⁵ Almost half of the carers Company evidence submission for epcoritamab for treating relapsed or refractory follicular lymphoma patients after three or more systemic treatments

surveyed reported having to reduce or stop working (either temporarily or permanently) since the patient's diagnosis.¹⁵

Most of the currently available treatment options are administered via infusions into a vein, a process that occurs over the course of several hours, requiring frequent patient monitoring visits over many months, generating a substantial temporal burden on both the patient, their carers and the health system at large. There is, therefore, a need for effective drugs that convey deep and meaningful responses that can be administered by a more convenient mode of administration.

There is limited reporting on the economic burden of FL in the UK. A 2018 report, based on patients with FL diagnosed between 2004 and 2011 and followed until 2015, reported an average lifetime cost to the healthcare system of £6,165 to £63,894 per patient.³⁵ Prevalence-based analysis estimated the annual treatment cost for FL at £60-65 million, approximately 10% of the NHS's annual budget for haematological cancers.³⁵ The scale of this economic burden in part will be because patients at later lines have no therapeutic options resulting in poor outcomes and high levels of healthcare resource utilisation. Indeed, of the patients reaching 4L+ treatment in the Haematological Malignancy Research Network (HMRN) data set, ■■■% of patients required inpatient admission with overnight stays.⁵ On average, patients required overnight stays for ■■■ days over each 28-day cycle.⁵

1.3.4 Epidemiology

FL accounts for approximately 6.2% of all haematological malignancies and for approximately 35% of all NHL and 70% of indolent lymphomas diagnosed in the United States and Western Europe, making it the second most commonly diagnosed lymphoma.^{36,37} Approximately 2,330 people per year in the UK are diagnosed with FL with the average age of diagnosis being 67 years.³⁶ The HMRN is a collaborative network of NHS clinicians and researchers situated across 14 hospitals across the UK, established to provide UK generalisable data for haematological cancers and their precursor conditions diagnosed using the WHO classification at a single hematopathology lab. Between 2010 – 2019, the HMRN reported the annual incidence

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rate of FL to be 3.6 per 100,000, with similar rates observed in men and women (3.5 vs 3.6, respectively).³⁶ The reported five and ten year prevalence in the UK is reported as 11,080 and 18,200, respectively.³⁶

1.3.5 FL grading and staging

1.3.5.1 Grading FL

In 2022, the World Health Organisation classified FL into four grades depending on the number of centroblasts identified via high power field (hpf) microscopy, with these grades being associated with clinical outcomes. Grade 1 FL has 0 to 5 centroblasts/hpf, Grade 2 FL has 6 to 14, Grade 3 can be further classified into Grade 3a, in which centrocytes are present and Grade 3b in which centroblasts present in sheets.³⁷

1.3.5.2 Staging FL

The anatomical extent (disease stage) of FL is determined by the Lugano classification system using fluorodeoxyglucose (FDG) – positron emission tomography (PET) scans, and an adaptation of the Ann Harbor staging system (Table 4).

Table 4. Lugano staging system for lymphoma

Stage	Involvement	Extra-nodal Status
Stage I	One node or group of adjacent nodes	Single extra-lymphatic site in the absence of nodal involvement
Stage II	Two or more nodal groups, same side of diaphragm	Extra- lymphatic extension from a nodal site with or without involvement of other lymph nodes
Stage III-1	Nodes on both side of the diaphragm; nodes with involvement of spleen/splenic, hilar, coeliac, portal nodes	N/A
Stage III-2	Nodes on both side of the diaphragm; nodes with spleen involvement/ involvement of the para-aortic, iliac, inguinal or mesenteric nodes.	N/A
Stage IV	Diffuse or disseminated involvement of one or more extranodal organs	N/A

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1.3.5.3 Prognosis

The FL international prognostic index (FLIPI) was developed based on the clinical characteristics of 4,167 patients diagnosed with FL and validated on a further 919 patients.³⁸ The FLIPI classifies patients into one of three categories; low risk, intermediate risk and high risk, based on five adverse prognostic factors; age > 60, Ann Arbor stage III/IV, haemoglobin (Hb) level <120 g/L, number of nodal sites >4 and elevated serum lactate dehydrogenase (LDH) levels. In 2009, the FLIPI-2 score was developed; this retained age and Hb level and added bone marrow involvement, elevated levels of beta-2-microglobulin and nodal masses >6cm for prognostic risk classification.^{39,40} FLIPI and FLIPI-2 are frequently used to inform the clinical prognosis of FL, but not to guide therapy.

FL patients are at high risk of relapse (lymphoma returning after successful treatment)¹¹ or refractory disease (lymphoma that doesn't respond to treatment), with FL becoming increasingly refractory to treatment and more likely to relapse sooner after each line of therapy.¹² Consequently, overall and progression free survival (OS and PFS) decrease significantly after first relapse and with each subsequent relapse.^{3,13} Recent HMRN data indicates that the prognosis for patients at 4L+ is poor, with OS reported at ■ months and PFS at ■ months.

1.3.5.4 Response Criteria

The Lugano classification system includes the Lymphoma Response to Immunomodulatory Therapy Criteria (LYRIC), developed specifically to evaluate response to immune-based treatment (Table 5).

Table 5. LUGANO and LYRIC interpretation criteria[†]

	LUGANO/ LYRIC
Complete Response (CR)	Positron emission tomography (PET)/ Computerised tomography (CT) scan: Deauville score (DS) [†] of 1,2,3 with or without residual mass Or CT: target nodes/nodal masses must regress to 1.5cm in longest diameter
Partial Response (PR)	PET/CT: DS 4 or 5 with reduced uptake compared with baseline and residual masses of any size Or CT: ≥50% decrease in sum of product of diameters (SPD) of up to 6 target measurable nodes and extranodal sites
Progressive disease (PD)	PET/CT: DS 4 or 5 with an increase in intensity of uptake from baseline and/or new FDG-avid foci consistent with lymphoma at interim or end of treatment (EoT) Or CT: an individual node/lesion must be abnormal with longest diameter > 1.5 cm and increase by ≥50% from product of the perpendicular diameter nadir and an increase in longest or short diameter from nadir 0.5 cm for lesions ≤ 2 cm 1.0 cm for lesions > 2 cm In the setting of splenomegaly, the splenic length must increase by >50% of the extent of its prior increase beyond baseline. If no prior splenomegaly must increase by ≥2 cm from baseline New or recurrent splenomegaly AND/OR involvement of the bone marrow. New or clear progression of preexisting non measured lesions Regrowth of previously resolved lesions A new node >1.5 cm in any axis or a new extranodal site > 1.0 cm in any axis; if <1.0 cm in any axis its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma: IR (1): ≥ 50% increase in SPD IR (2): < 50% increase with SPD with a. New lesion(s) or b. ≥50% increase in product of the perpendicular diameters (PDD) IR(3): Increase in FDG uptake without concomitant increase in lesion size meeting criteria for PD

[†] The Deauville five-point scale is an internationally recommended scale for clinical reporting and clinical trials using FDG PET-CT for staging and assessment of treatment of HL and NHL.

CR, complete response; CT, computerised tomography; DS, Deauville scores; EoT, end of treatment; FDG, fluorodeoxyglucose; PD, partial response; PDD, product of perpendicular diameters; PET, positron emission tomography; PR, partial response; SPD, sum of product of diameters

1.3.6 Treatment Pathways

There is no standardised treatment pathway for FL, especially as patients move to later lines of treatment. Instead, treatment is tailored to the patient and depends on their previous treatment and responses. About 20% of patients experience disease progression within 2-years of starting immune-chemotherapy.¹² At 4L+, treatment options are limited, with patients frequently receiving further rituximab-based treatments (Figure 1).

1.3.6.1 Treatment of early-stage FL (Stages I and II)

Conventionally, early-stage FL comprising stage I-II disease (where the involved nodes are contiguous and can be easily encompassed within a radiation field) has been treated with local radiotherapy. Observation without involved site radiotherapy (ISRT) can be considered for people with limited stage FL who have undergone localised excision and where there may be concerns about radiotherapy of a particular site. Patients with early-stage disease that is discontinuous or are otherwise unsuitable for radiotherapy should be managed as advanced stage disease.⁴²

1.3.6.2 Treatment of advanced-stage FL (Stages III and IV)

1.3.6.2.1 First-line treatment

The British Society of Haematology (BSH) guidelines recommends that patients with symptomatic high tumour burden FL are treated with an anti-CD20 antibody (rituximab or obinutuzumab) in combination with chemotherapy (-cyclophosphamide, doxorubicin, vincristine and prednisolone [-CHOP], or – cyclophosphamide, vincristine and prednisolone [-CVP], or bendamustine) depending on patient characteristics and the evaluation of the treating clinician. R- and O- CHOP chemotherapies are burdensome for both the patient involved and the healthcare system, requiring cannulation and IV administration. Rituximab (or obinutuzumab, whichever had been used for induction) maintenance can also be considered for patients who have responded to induction therapy and can prolong PFS.

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1.3.6.2.2 2L and 3L line treatment

There is no defined treatment pathway for individuals with advanced R/R FL at 2L and beyond, instead treatment strategies are informed by the previous treatments a patient has received, along with age, fitness and available options. In cases where patients have experienced a relatively long remission period, the 2020 BSH guidelines recommend a repeat rituximab therapy with the same chemotherapy as previously administered at earlier lines of treatment.⁴² In cases where a shorter remission is experienced, rituximab with an alternative chemotherapy is recommended. In cases where patients are rituximab-refractory, the BSH guidelines state bendamustine in combination with obinutuzumab (OB) can be considered, followed by obinutuzumab (O) maintenance.⁴² OB is seldom used in UK clinical practice.²

Some patients may be eligible for a stem cell transplant as part of their 2L and 3L treatment. High dose chemotherapy with autologous stem cell transplant (HDT-ASCT), can be considered for the relatively small proportion of fitter patients, where best outcomes have been observed in 2L.⁴²

The 2021 European Society for Medical Oncology (ESMO) guidelines also recommend a rituximab-based approach to managing R/R FL, with consideration for rituximab maintenance therapy if it had not been previously used. Lenalidomide and rituximab (R²) combination therapy is also an option for patients, especially if they had a short remission to immune-chemotherapy or a short relapse after chemotherapy and may therefore be regarded as chemo-refractory.⁴³ The ESMO guidelines recommend OB and HDT-ASCT as options for patients at first relapse after a rituximab-containing immune-chemotherapy.⁴³

1.3.6.2.3 4L treatment and beyond

At 4L+, there is no standard of care for the treatment of FL, with very limited treatment options available for patients. In routine care, a treatment strategy based upon their prior treatments or best supportive care is usually offered. Patients rechallenged with a prior treatment regimen often experience poor outcomes due to acquired treatment

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resistance. This is particularly the case if the previous therapy resulted in a non-durable remission.²

Given the current lack of treatment options at 4L+, clinical trials are also considered for younger and fitter patients at this stage, in many cases requiring referral to tertiary centres adding inconvenience for patients and carers or resulting in inequality of access for those who are unable to travel.

Despite the significant unmet need in this heavily pre-treated population, there have been limited innovations in recent years that have met the standard required by NICE for approval, with no positive recommendations made since 2020. Table 6 contains a list of terminated NICE appraisals or treatments not recommended by NICE for R/R FL since the last positive recommendation in 2020.

Table 6. Terminated appraisals and technologies that were not recommended since 2020

Treatment	Guidance No.	Year	LOT	Outcome
Tazemetostat	GID-TA11399 ⁴⁴	2024	3L+	Discontinued
Zanubrutinib with obinutuzumab	TA978 ⁴⁵	2024	3L+	Terminated appraisal
Axicabtagene ciloleucel	TA894 ¹⁹	2023	4L+	Not recommended
Mosunetuzumab	TA892 ¹⁶	2023	3L+	Not recommended
Tisagenlecleucel	TA842 ⁴⁶	2022	3L+	Terminated appraisal
Ibrutinib	GID-TA11238 ⁴⁷	2022	R/R	Discontinued
Duvelisib	TA717 ⁴⁸	2021	3L+	Terminated appraisal

FL, follicular lymphoma; LOT, line of therapy

1.3.6.3 NICE-approved treatments

Current NICE recommendations for the management of FL are focused on anti-CD20 monoclonal antibody-based therapies and are presented in Table 7. The current treatment strategies adopted for FL patients are summarised in Figure 1.

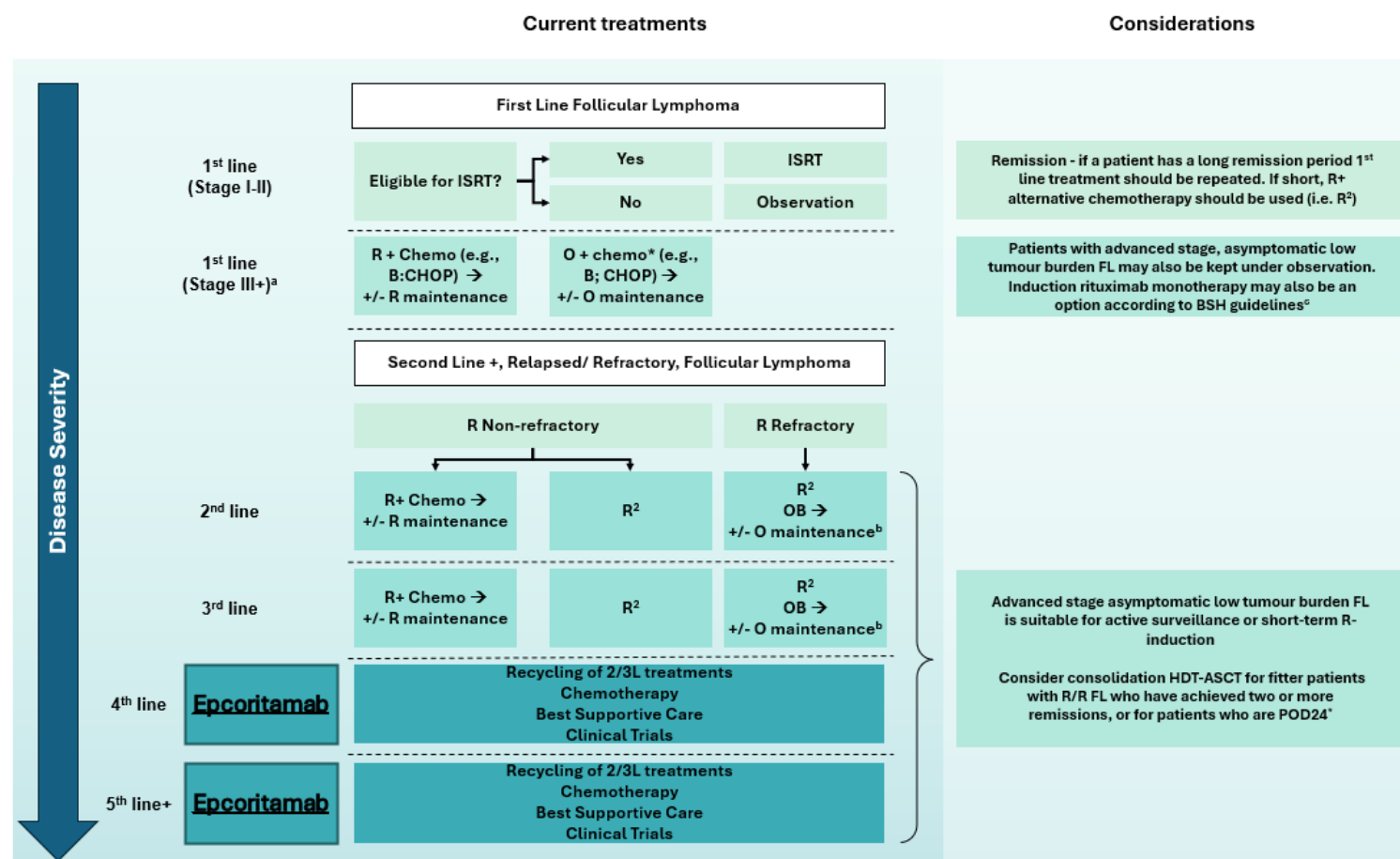
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Table 7. Positive NICE recommendations

Treatment	Guidance No.	Year	Indication	LOT
Obinutuzumab with bendamustine	TA629 ¹⁸	2020	FL patients with prior rituximab treatment	2L+
Lenalidomide with rituximab (R ²)	TA627 ¹⁷	2020	Previously treated Grade 1-3A FL	2L+
Obinutuzumab in combination with chemotherapy	TA513 ⁴⁹	2018	First line treatment of advanced FL	1L+
Rituximab	TA243 ⁵⁰	2012	First line treatment of Stage III- IV FL	1L+
Rituximab	TA226 ⁵¹	2011	First line maintenance treatment	1L+

FL, follicular lymphoma; LOT, line of therapy

Figure 1. Proposed position of epcoritamab in the current FL treatment pathway



a – patients with advanced stage FL are assessed against the Groupe d'Etude des Lymphomes Folliculaires (GELF) criteria to ascertain if they require treatment. b – maintenance at relapse is usually only considered if maintenance was not given after 1L treatment. c – though recommended by the BSH, rituximab monotherapy does not have UK authorisation for this indication and is not currently commissioned by NHS England for this purpose.

Note: Best supportive care is not considered a relevant comparator for epcoritamab as patients requiring best supportive care are not expected to be fit enough to receive an active intervention. O-chemo is only approved for patients with a FLIPI score of 2 and above. "Chemo" included R-CHOP (Rituximab + cyclophosphamide, doxorubicin hydrochloride, vincristine sulphate and prednisone), CVP (cyclophosphamide, vincristine sulphate and prednisone) and bendamustine. Active surveillance is suitable for patients with late stage, asymptomatic low tumour burden FL. ISRT can be repeated at treatment, dependent on initial dosing. R-mono therapy can be used at relapse, although this is uncommon in the UK. BSH, British Society of Haematology; HDT-ASCT, high dose chemotherapy with autologous stem cell transplant; ISRT, involved-site radiation therapy; O, obinutuzumab; OB; obinutuzumab with bendamustine; POD24, disease progression or relapse within 24 months of initial treatment ; R, rituximab; R², rituximab + lenalidomide; R-CHOP, rituximab, cyclophosphamide, doxorubicin hydrochloride and vincristine sulphate

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1.3.7 Unmet need in R/R FL

Patients with FL will often receive several treatment courses over several years, with shortening durations of response being observed after each line of therapy; at 1L, 62% of patients still respond to treatment after 5-years, decreasing to 39% and 24%, respectively, for those on 2L and 3L treatments.⁴

Patient prognosis is particularly poor once a patient reaches 4L+ treatment, by which time there are very limited treatment options available. FL at this stage is often resistant to conventional treatment and can be considered an end-of-life disease, with an estimated median OS for patients at 4L+ of less than a year (■■■ months) and median PFS of ■■■ months.⁵ Patients are often rechallenged with previously administered treatments. Response to these recycled treatments is often poor, with only approximately ■■■% of patients achieving a complete response (CR).⁵ Among responders, duration of response is typically very short.

Existing chemotherapy-based treatment options do not fully address the immune dysfunction associated with FL and are associated with well-documented toxicities. For example, repeating R-CHOP treatment is not feasible as it is associated with an increased dose-dependent risk of cardiotoxicity.²⁰

There is also a considerable humanistic burden associated with the current FL treatment pathways. Fear of cancer recurrence or progression is considered the most common unmet need by patients with cancer.⁵² Among cancer survivors and patients with active cancer, 59% and 19% report a moderate or severe fear of cancer reoccurrence (FCR), respectively.⁵³ An estimated 46% of patients with lymphoma or CLL fear disease progression or relapse, with higher rates of anxiety being reported in patients experiencing relapse than those who are in remission or disease free, issues which are particularly pertinent in 4L+ R/R FL where median PFS is reported at only ■■■ months in patients with 4L+ R/R FL.^{5,54}

Current chemotherapy treatments are administered via infusion into a vein, which is given slowly over a few hours for the first treatment to prevent side effects.⁵⁵ Patients treated with R-CHOP should have a blood test either the day of or the day before
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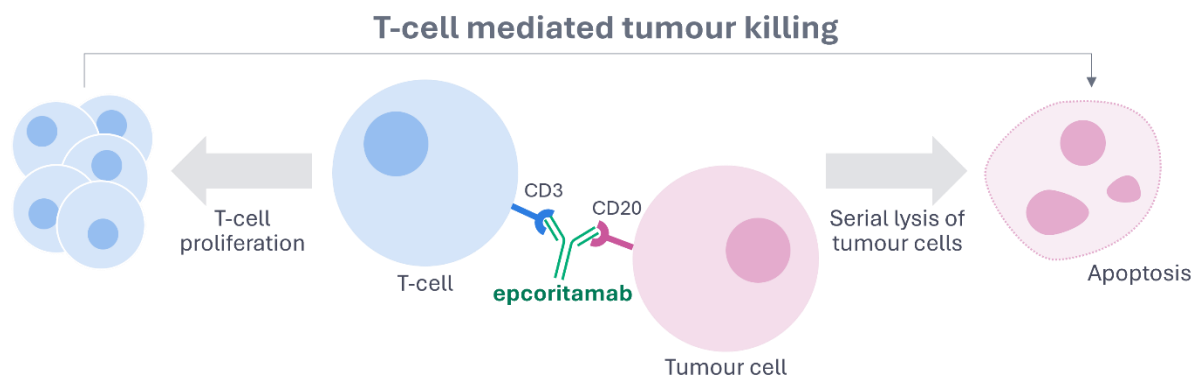
treatment and so may require two trips to a healthcare setting. Therefore, current treatments are time intensive, preventing both patients and carers from conducting their normal daily activities. A recent report by the Lymphoma Coalition found that 23% of individuals (carers, friends or family members of patients with FL) had to stop work, either permanently or temporarily, with a further 22% reporting that they had to reduce their work.¹⁵

There is therefore, a significant unmet need for novel interventions that deliver deep and durable response in this high-risk, heavily pre-treated population who have such poor outcomes.⁵ An alternative mechanism of action to conventional chemotherapy-based treatments would offer patients and clinicians choice as well as hope for a new treatment beyond recycling therapies to which a patient has already failed to maintain a durable response. Likewise, patients with FL require a treatment that can be delivered via a more convenient mode of administration and has a tolerable safety profile, which will offer patients with a much needed alternative to current treatments options.

1.3.8 Epcoritamab

Epcoritamab is a humanised IgG1-bispecific antibody that binds to the CD20 B-cell antigen and the CD3 T-cell antigen, inducing specific T-cell activation and T-cell mediated killing of CD20 expressing cancer cells (Figure 2). As such epcoritamab requires the binding of both B and T-cells to initiate cell death, circumventing the cytotoxicity that can be associated with conventional CD20-targeting therapies. Of note, epcoritamab binds an alternate CD20 epitope to that targeted by rituximab and obinutuzumab. Epcoritamab has proven benefits in treating other haematological malignancies and was recently recommended for the treatment of DLBCL in adults who have received two or more systemic treatments (and where they have either previously received or are unable to receive polatuzumab vedotin) by NICE (TA954, recommended March 2024).⁸

Figure 2. Mechanism of action of epcoritamab



Adapted from Aldoss et al. 2017⁵⁶

1.3.9 Proposed position for Epcoritamab

Epcoritamab is proposed for use as a 4L+ treatment for R/R FL. As described throughout Section 1, this is the patient population with the greatest unmet need; therefore, access to an innovative therapy and less invasive therapeutic options will address a key unmet need in patients facing a short life expectancy.

Currently, there are no treatments approved specifically for the treatment of 4L+ patients. As outlined in Section 2, epcoritamab has the potential to meet this unmet need, providing deep and clinically meaningful responses, delivering improved OS and PFS.

Epcoritamab offers an alternative to current CD20-based therapies, conveying its benefits through an alternate mode of action to offer increased therapeutic options. In the EPCORE NHL-1 study, epcoritamab demonstrated a manageable safety profile that clinicians will already be familiar with in their experience of treating DLBCL with epcoritamab under NICE approval. Through its subcutaneous administration, epcoritamab reduces the burden on both the healthcare system and patients. These injections are notably faster, less invasive and require less monitoring than traditional intravenous treatments used for 4L+ FL therapies.

1.4 Equality considerations

It is not anticipated that the provision (or non-provision) of epcoritamab within its licensed indication would exclude from consideration any people protected by equality legislation, lead to a recommendation that has a different impact on people protected by equality legislation or lead to recommendations that will have adverse impact on people with a particular disability or disabilities.

However, as discussed previously, patients reaching 4L+ are more likely to receive experimental treatments within clinical trials than patients in earlier lines. As access to clinical trials might be more restricted in rural or deprived areas, patients with 4L+ R/R FL are likely to benefit from access to an efficacious therapy as part of routine commissioning.

2 Clinical effectiveness

Results from the EPCORE NHL-1 trial demonstrated that epcoritamab drives clinically meaningful response and survival outcomes in patients with 4L+ R/R FL

- Clinical evidence on the efficacy and safety of epcoritamab in patients with 4L+ R/R FL comes from EPCORE NHL-1: a phase 1/2, open-label, dose-escalation and expansion trial.
- The results of EPCORE NHL-1 reflect the target population for epcoritamab in line with the decision problem. UK clinical experts felt that EPCORE NHL-1 is generalisable to clinical practice; however, clinical experts noted that the trial studied a particularly unfit population with several risk factors.
- Durable OS was observed in this high-risk cohort and the median OS was [REDACTED] during follow-up (median follow-up of [REDACTED]). Median disease progression with epcoritamab in 4L+ R/R FL did not occur until [REDACTED].
- A best overall response (BOR) of complete response (CR) was achieved in [REDACTED] of patients in the 4L+ cohort. The overall response rate (ORR) was [REDACTED].
- Patient quality of life (QoL), as assessed by the Functional Assessment of Cancer Therapy-Lymphoma Subscale (FACT-LymS) indicated that HRQoL was maintained by epcoritamab treatment while an improvement was reported in outcomes from the EQ-5D-3L survey.

An unanchored match-adjusted indirect comparison (MAIC) demonstrated that epcoritamab provides substantial, statistically significant and clinically meaningful improvements in survival for people with 4L+ R/R FL compared with current treatment options

- A MAIC was conducted following the guidance described in Signorovitch et al, NICE TSD 18, and learnings from previous NICE TAs in R/R FL.^{16,17,19,57,58}
- MAICs were performed using individual patient data from the EPCORE NHL-1 trial compared against real-world UK data from HMRN, which reflects current 4L+ care in R/R FL.
- To maintain the precision of the indirect comparison, efforts were made to maintain an appropriate effective sample size (ESS) for decision making, by selecting the most clinically relevant variables for adjustment, in line with External Assessment Group (EAG) critique from previous appraisals in R/R FL and input from clinical experts.
- Improvements in OS and PFS following treatment with epcoritamab were both clinically and statistically significant compared with outcomes from treatment with current 4L+ care, with hazard ratios of [REDACTED] and [REDACTED], respectively.

- Population-adjusted results from the MAIC showed that patients treated with epcoritamab were more likely to achieve a CR and OR compared with patients treated with current 4L+ care:
 - CR: [REDACTED] for epcoritamab vs. [REDACTED] with current 4L+ care ([REDACTED])
 - ORR: [REDACTED] for epcoritamab vs. [REDACTED] with current 4L+ care ([REDACTED])

The overall safety profile of epcoritamab was considered manageable and acceptable in this FL population

- At least one TEAE was experienced by [REDACTED] of patients in the 4L+ cohort, [REDACTED] of which were considered related to epcoritamab but these events were largely manageable and consistent with the known safety profile of epcoritamab.
- Cytokine release syndrome (CRS) was reported in [REDACTED] of the 4L+ cohort. Immune effector cell-associated neurotoxicity syndrome (ICANS) events were reported in [REDACTED] of the 4L+ cohort. No clinical tumour lysis syndrome (CTLS) events were reported.

Epcoritamab is the first subcutaneous treatment available to patients with R/R FL after three or more lines of therapy, adding novel treatment options to a very limited treatment pathway

- Epcoritamab's novel mechanism of action is expected to provide significant benefits to patients with R/R FL at 4L+, offering clinically meaningful responses and durable survival while presenting a conveniently administered alternative to current 4L+ treatments, which mainly include chemotherapies.
- The introduction of epcoritamab is anticipated to both improve patient quality of life, and reduce strain on healthcare systems, by removing the need for burdensome and invasive IV treatments.

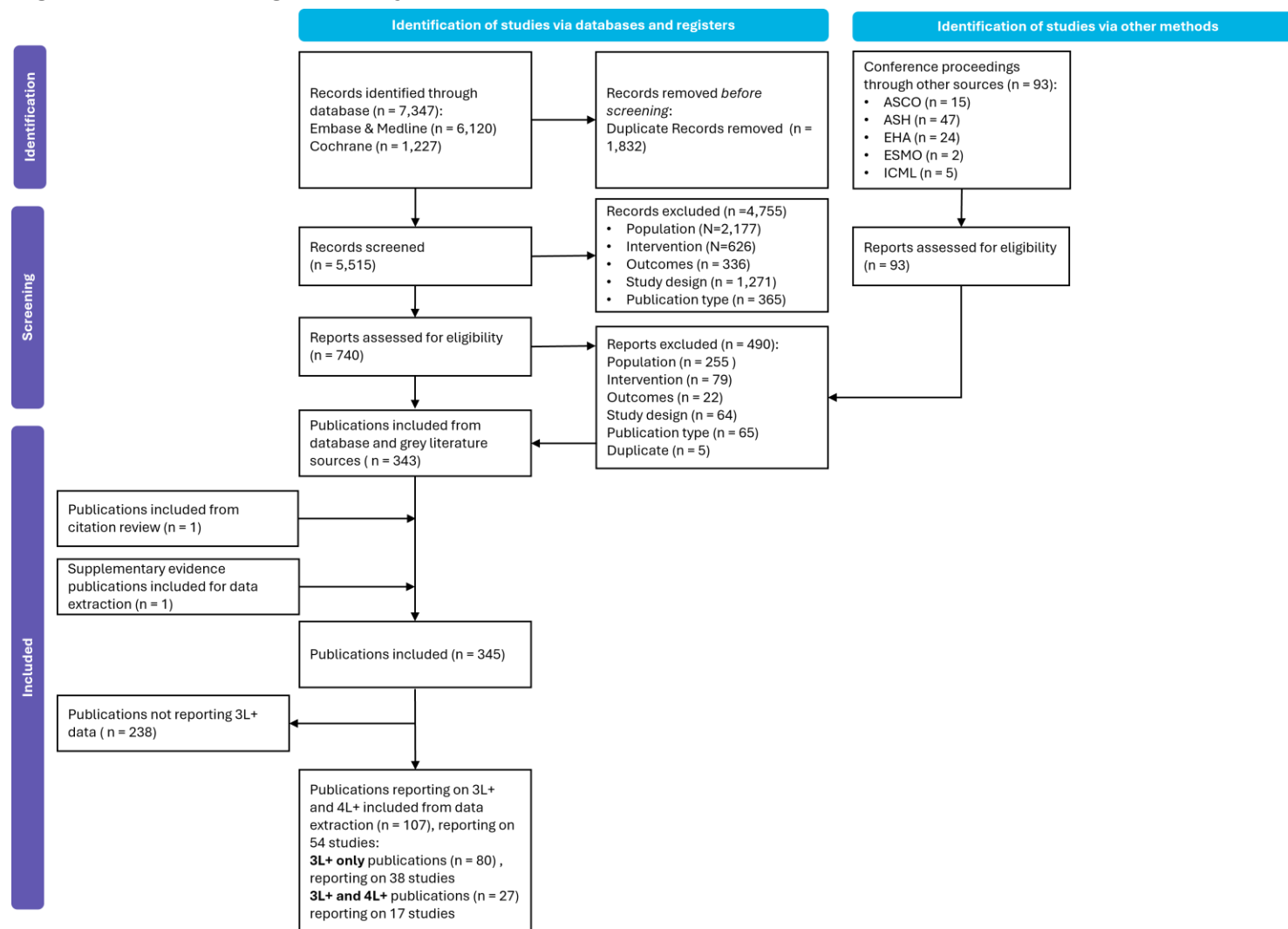
2.1 Identification and selection of relevant studies

A systematic literature review (SLR) was conducted to evaluate the efficacy and safety of treatments for adult patients with 3L+ and 4L+ relapsed/refractory follicular lymphoma (R/R FL). Appendix B reports the full details of the process and methods used to identify and select the clinical evidence relevant to the technology being evaluated.

Searches were originally run on 3 April 2023, and updated on 13 March 2024 and 7 November, 2024. Relevant studies were identified by searching the following databases: Medical literature analysis and retrieval system online (MEDLINE), Excerpta Medica database (Embase), Cochrane Central Register of Controlled Trials (CENTRAL) and Cochrane Database of Systematic Reviews (CDSR). Proceedings from the following conferences were also searched from 2020-2024: European Hematology Association (EHA), International Conference of Malignant Lymphoma (ICML) Annual meeting, American Society of Hematology (ASH), American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO) annual meeting. Conferences that are not indexed in Embase were hand searched. On-going trials were searched for entries up to 3 April 2023 in the clinicaltrials.gov, the EU clinical trials register, the WHO International Clinical Trials Registry Platform (ICTRP), the health Canada clinical trials database and European union electronic register of post authorisation studies.

After de-duplication, 5,515 publications were included for title and abstract screening, 740 of which were included for full-text screening; 345 met inclusion criteria. Of these, 238 publications did not report 3L+ data, resulting in 107 publications, reporting on 54 studies identified in the SLR. Of these 107 publications, 80 reported on 38 studies presenting 3L+ data only, the remaining 27 publications reported on 17 studies reporting on both 3L+ and 4L+ (Figure 3).

Figure 3. PRISMA diagram for systematic literature review



Note: The SLR identified “3L+ only” and “3L+ and 4L+” reporting for the UNITY trial, and as such the number of publications in the PRISMA = 55, rather than 54. ASCO, American Society of Clinical Oncology; ASH, American Society of Hematology; EHA, European Hematology Society; ESMO, European Society for Medical Oncology; ICML, International Conference on Malignant Lymphoma (ICML)

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2.2 List of relevant clinical effectiveness evidence

The clinical SLR was conducted from a global perspective and as such identified comparators that are not applicable to the NICE decision problem. A list of the included studies can be found in Appendix B. The clinical SLR identified one clinical trial for epcoritamab in patients with 3L+ R/R FL, a summary of which can be found in Table 8.

EPCORE NHL-1 (NCT03625037), was a multi-stage, multi-cohort study that provided clinical evidence for the safety and efficacy of epcoritamab as a treatment for adults with relapse or refractory B-cell lymphomas, including FL. Table 9 provides a summary of the EPCORE NHL-1 trial, and the included cohorts.

Table 8. Clinical effectiveness evidence study

	EPCORE NHL-1 (NCT03625037)
Study design	Open label, multicentre, phase 1/2 trial in patients aged 18 years or older with relapsed, progressive and/or refractory disease including a dose Escalation Part and Expansion Part followed by a dose Optimisation part.
Population	Patients with relapsed, progressive or refractory B-cell lymphomas, including FL. The expansion part of the trial was initiated with parallel enrolment in three cohorts of patients with aNHL (i.e. LBCL), iNHL and MCL. This submission considers the dose expansion part for FL 1-3A patients only from the iNHL cohort, segregated into total population and 4L+ patients. This submission also provides efficacy data for the 4L+ population of the Optimisation Part of EPCORE NHL-1.
Intervention(s)	Epcoritamab, administered via subcutaneous injection
Comparator(s)	N/A
Indicate if study supports application for marketing authorisation	Yes
Indicate if study used in the economic model	Yes
Rationale if study not used in model	N/A
Reported outcomes specified in the decision problem	Primary endpoint: ORR determined by Lugano criteria as assessed by IRC Secondary endpoints: Response rates determined by Lugano and LYRIC assessments OS

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	EPCORE NHL-1 (NCT03625037)
	ORR (CR) PFS assessed by Lugano and LYRIC criteria Patient reported outcomes (FACT-Lym and EQ-5D-3L) Safety outcomes (i.e. adverse events [AEs], hospitalisations and cytokine measures).
All other reported outcomes	TTNT DOR, DOCR, TTR assessed by LYRIC and Lugano criteria Rate of MRD negativity

aNHL, aggressive non-Hodgkin lymphoma; CR, complete response; DOCR, duration of complete response; DOR, duration of response; FACT-Lym, functional assessment of cancer therapy – lymphoma; iNHL, indolent non-Hodgkin lymphoma; IRC, independent review committee; LBCL, large B-cell lymphoma; LYRIC, lymphoma response to immunomodulatory therapy criteria; MCL, mantle cell lymphoma; MDR, minimal residual disease; MZL, marginal zone lymphoma; ORR, overall response rate; PFS, progression free survival; SLL, small lymphocytic lymphoma; TTNT, time to next treatment; TTR, time to response

Table 9. EPCORE iNHL trial design

	Dose Escalation (Phase 1)	Dose Expansion (Phase 2)	Dose Optimisation (Phase 2)
Objectives	To determine the maximum tolerated dose (MTD) and the recommended Phase 2 dose (RP2D), as well as to establish the safety profile of epcoritamab in patients with relapsed or refractory B-cell lymphoma.	Additional patients will be treated with epcoritamab, at the RP2D and the purpose is to further explore and determine the safety and efficacy of epcoritamab.	Evaluate alternative priming and intermediate dose regimens of epcoritamab in patients with: DLBCL, FL and MCL
Cohorts	ONE	THREE cohorts of patients with aNHL • LBCL • iNHL (n=155) • MCL	THREE cohorts of patients with: • FL grades 1-3A • DLBCL • MCL
Description of Cohort Relevant to Submission	N/A	iNHL cohort includes • 3L+ FL 1-3A (n=128) • MZL (n=23) • SSL (n=4) Only 3L+ FL 1-3A is relevant to this submission	3L+ FL grades 1-3A includes • Arm A (n=86) • Arm B (n=6) Arm B is not relevant to this submission as the 6mg Day 15 step-up dose is different from that in the marketing authorisation application
AbbVie Positioning	N/A	4L+ FL 1-3A (n=81)	4L+ FL 1-3A (n=41)
Dosages		Cycle 1 (D1: 0.16mg, D8: 0.8mg, D15:48mg)	Cycle 1 (D1: 0.16mg, D8: 0.8mg, D15 3 mg or 6 mg, D22:48 mg)
Data presented in	N/A	Data pertaining to the 4L+ FL cohort (n=81) is presented in Sections 2.8, 2.9,2.10, 2.11 . Data pertaining to the 3L+ FL 1-3A cohort (n=128) is presented in Appendix M	Data pertaining to the C1-Opt 4L+ cohort (n=41) is provided to give additional context and is presented in Section 2.14 . Data pertaining to the C1-Opt 3L+ cohort (n=86) is presented in Appendix M
Data cutoff	N/A	██████████	8 January 2024
Median follow-up	N/A (included in Dose Expansion)	██████████	5.7 months

Emboldened cohorts are represented as part of this submission.

DLBCL, diffuse large B-cell lymphoma; iNHL, indolent non-Hodgkin lymphoma; LBCL, large B-cell lymphoma; MZL, mantle cell lymphoma; RP2D, recommended Phase 2 dose; SSL, small lymphocytic lymphoma.

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2.3 EPCORE NHL-1

EPCORE NHL-1 was a phase 1/2 open-label, multi-centre, multi-national trial evaluating the efficacy and safety of epcoritamab in various forms of non-Hodgkin lymphoma (B-NHL), including FL and DLBCL. The trial was conducted in three parts: a dose escalation part, an expansion part and an optimisation part. Table 9 above provides an overview for trial orientation.

The key evidence for this submission comes from the dose expansion phase of the trial, designed to evaluate the efficacy and safety of epcoritamab in patients with relapsed, progressive or refractory FL, who have had at least two lines of prior therapy.

2.4 EPCORE NHL-1 Dose Expansion Cohort

2.4.1 Summary of Methodology

A summary of the dose expansion part of EPCORE NHL-1 is presented in Figure 5.

The expansion part of the trial was initiated with parallel enrolment in three cohorts with distinct B-cell lymphoma subtypes:

- R/R aNHL cohort (LBCL)
- **R/R iNHL cohort (including FL Grade 1-3A)**
- R/R MCL cohort

These cohorts were treated with the recommended phase 2 dose (RP2D) of epcoritamab. The iNHL cohort is the focus of this submission as this contains the population consistent with the decision problem and the licensed indication for epcoritamab relevant to this submission

The iNHL cohort was conducted in two stages, illustrated in Figure 5. Only patients with R/R 3L+ FL Grade 1-3A were enrolled into the iNHL cohort in Stage 1. Following an interim futility analysis, additional patients with iNHL were enrolled in Stage 2, including individuals with other iNHL subtypes (small lymphocytic lymphoma [SLL] and marginal

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zone lymphoma [MZL]). An overview of the trial methodology, including the key eligibility criteria, is provided in Table 10.

In total, there were 155 patients in the iNHL cohort, of which 128 patients were 3L+ FL 1-3A patients (detailed in Appendix M) and 81 were 4L+ FL patients (Figure 4 & Figure 5). The 4L+ population was a pre-specified subgroup of the EPCORE NHL-1 trial, and the safety and efficacy data for these participants are presented as part of this submission. This cohort is referred to herein as “4L+ FL.”

Figure 4. Patient enrolment into the EPCORE- NHL1 trial (Dose Expansion cohort)

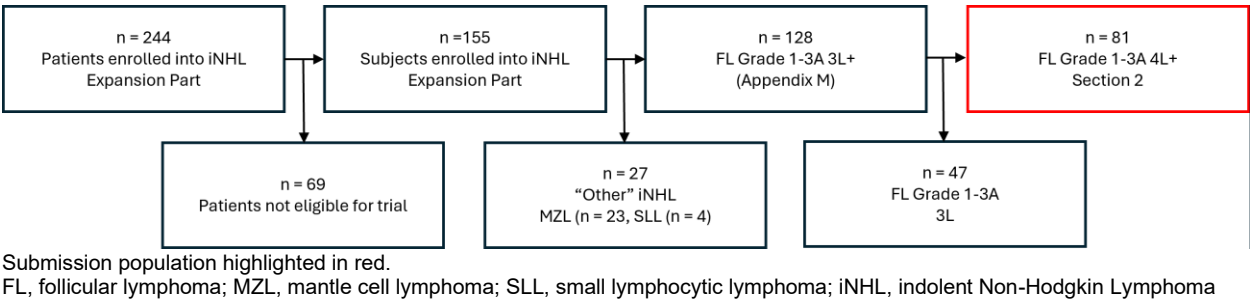
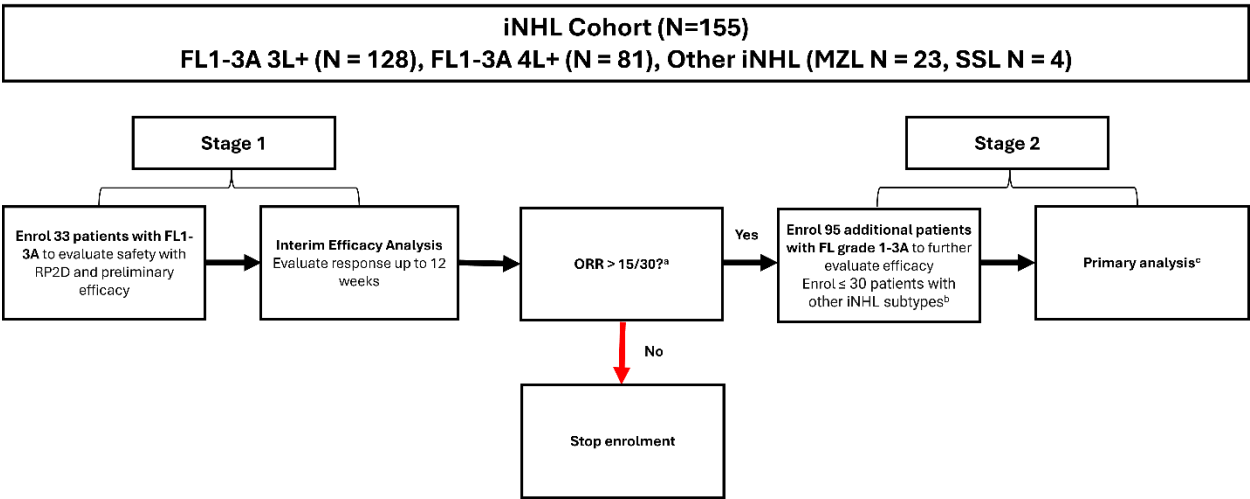


Figure 5. Overview of the EPCORE NHL-1 expansion part

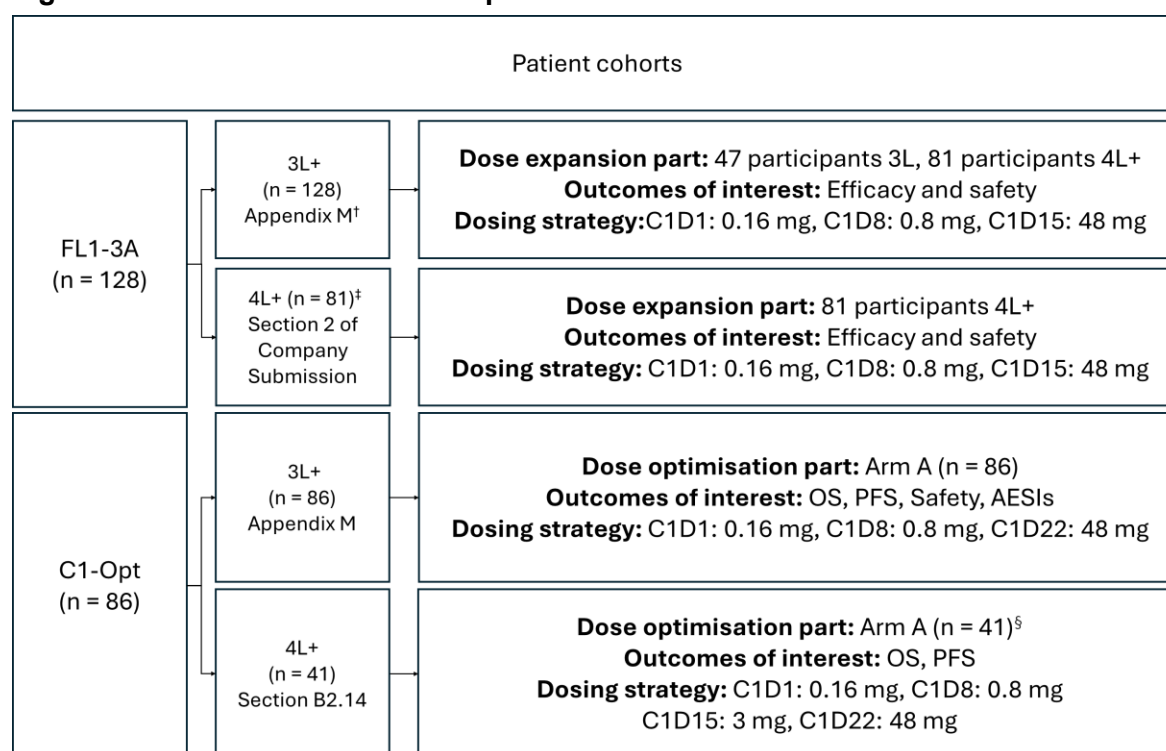


Stage 1 only recruited patients with relapse/refractory follicular lymphoma who were followed up at 12 weeks. During the interim analysis, the futility criteria was exceeded (no more than 15/30 responders) and an additional 95 patients were enrolled into Stage 2. a. For the interim analysis, response was determined by Lugano criteria assessed by the investigator and sponsor based on available data (e.g. efficacy, safety, pharmacodynamic and biomarkers). The denominator for the interim analysis accounts for a 10% dropout rate. b. Other subtypes include MZL and SLL. d. For primary analysis, response was determined by Lugano criteria as assessed by the IRC. iNHL, indolent non-Hodgkin lymphoma; RP2D, recommended phase 2 dose Source: Adapted from Figure 1, AbbVie, iNHL, CSR 2023.

2.5 Overview of data presented within this submission

As part of this submission, data from both the Dose Expansion and Dose Optimisation parts of the EPCORE NHL-1 trial are presented. The 4L+ FL Dose Expansion cohort is presented in the main Company Submission as is from the pivotal study and informs the population described in the decision problem. Data for the 4L+ cohort of the C1-Optimisation part of the trial is presented to give further context on the safety and efficacy of epcoritamab and is presented in Section 2.14. Data pertaining to the full trial population (3L+ FL) for the dose expansion cohort can be found in Appendix M for completeness. A summary of presented data, and its location in the company submission dossier is presented in Figure 6.

Figure 6. Overview of cohort data presented



†COVID and non-COVID modified data for the full trial population are presented in the Appendix M

‡ The COVID-unmodified data from the 4L+ cohort is presented in Appendix M

§ Data pertaining to Arm A of the C1-Opt part of EPCORE NHL-1 is presented throughout the document as its dosing regimen aligns with the market authorisation for epcoritamab.

Table 10. Summary of EPCORE NHL-1 methodology

Trial Name	EPCORE NHL-1 (NCT03625037)	
Location	EPCORE NHL-1 was a multicentre trial conducted at 85 locations across: Australia, US, Canda, Denmark, Finland, France, Germany, Italy, republic of Korea, Netherlands, Poland, Singapore, Spain, Sweden and the United Kingdom	
Trial design	EPCORE NHL-1 was a phase 1/2 open-label, dose escalation and expansion trial	
Eligibility criteria for patients	Inclusion criteria: • Over the age of 18 years • Have documented CD20+ mature B-cell neoplasm according to WHO classification • Have one measurable site of disease based on CT/MRI • Patients must have FL • Patients must have relapsed, progressive and/or refractory disease • Relapsed, progressive and/or refractory disease following treatment with an anti-CD20 monoclonal antibody (rituximab) • Patients must have exhausted or are ineligible for all standard therapeutic options • Patients with indolent lymphoma must have a need for treatment initiated based on symptoms of disease burden • ECOG performance status 0,1, or 2 • Lymphocytes $<5 \times 10^9/L$ • Platelet count $\geq 75 \times 10^9/L$ • Absolute neutrophil count $\geq 1.0 \times 10^9/L$ • At least 4 weeks from last dose of unconjugated anti-CD20 targeting therapy • At least 12 weeks from last dose of radio-conjugated/ toxin conjugated compound • At least 4 weeks from last dose of investigational monoclonal anti monoclonal antibodies, investigational chemotherapy or other experimental therapy. • Resolution of toxicities for prior therapy to a grade that does not contraindicate trial.	Exclusion criteria: • Patients diagnosed with CNS lymphoma or have known CNS involvement. • Past or current malignancy • AST or ALT $>3 \times ULN$ • Total bilirubin $>1.5 ULN$ • Known clinically significant cardiac disease • Chronic ongoing infectious disease • Confirmed history or current autoimmune disease • Seizure disorder requiring therapy • Any prior CD3xCD20 therapy • Prior treatment with chimeric CAR-T therapy within 30 days • Eligible for curative inessive salvage therapy followed by high dose chemotherapy with HSCT rescue • HCST within 100 days prior to the first epcoritamab administration • Active hepatitis B or C. • Known HIV infection

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	• If receiving glucocorticoid treatment at screening, treatment must be tapered down and administered with a maximum of 25 mg daily. • Before the first dose of epcoritamab during the trial and for 12 months after the last administration of epcoritamab. • Not of childbearing potential; premenarchal postmenopausal (>45 years of age with amenorrhea for at least 12 months or any age with amenorrhea for at least 6 months and a serum follicle stimulating hormone [FSH] level >40 IU/L or mIU/mL); permanently sterilised or otherwise incapable of pregnancy. • Of childbearing potential and practicing a highly effective method of birth control consistent with local regulations regarding the use of birth control methods for patients participating in clinical trials. • Males who are sexually active with a woman of child-bearing potential must agree to use barrier method of birth control and for 12 months after receiving the last dose of epcoritamab • Women must agree not to donate eggs for the purpose of assisted reproduction during the trial and for 12 months afterwards. • Males must not donate sperm during the trial and for 12 months afterwards. • Patients must provide written consent.	• Exposed to live or live attenuate vaccine within 3 weeks prior to ICF signing • Pregnancy or breast feeding • Patient has any condition where, in the opinion of the investigators, participation would not be in the best interest of the patient • Patients have a known hypersensitivity to allopurinol or rasburicase
Trial drugs and method of administration	Epcoritamab is administered as a subcutaneous injection. • For the pivotal FL Dose Expansion cohort of the EPCORE NHL-1 trial, the dosing regimen consisted of an initial priming phase of 0.16 mg (C1D1) followed by an intermediate dose of 0.8 mg (C1D8), and a full dose of 48 mg C1D15/C1D22. Following this, epcoritamab at 48 mg was administered on days 1, 8, 15 and 22 for cycles 2 and 3, days 1 and 15 for cycles 4 – 9 and day 1 of Cycle 10 + until progression or unacceptable toxicity. Patients were hospitalised for 24 hours following the first full dose of epcoritamab. • For the C1-optimisation part of the EPCORE NHL-1 trial (discussed in Section 2.14), the dosing regimen consisted of an initial priming dose of 0.16 mg (C1D1) followed by a first intermediate dose of 0.8 mg (C1D8) and a second intermediate dose of 3 mg (C1D15), and a full dose of 48 mg on C1D22. Following this, epcoritamab was administered on days 1, 8, 15 and 22 for cycles 2 and 3, days 1 and 15 for cycles 4 – 9 and day 1 of Cycle 10 + until progression or unacceptable toxicity. Hospitalisation was not mandated for subjects in this cohort, but subjects were to remain in close proximity to the treatment facility (i.e., within 30 minutes distance) for 24 hours after the first full dose of epcoritamab (i.e., C1D22).	

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Permitted and disallowed concomitant medication	With the exception of anti-lymphoma therapy, concomitant medicines were allowed to provide adequate care.	
	Permitted concomitant medications: • Supportive therapy for CTLS and CRS • Prophylactic antibiotics, antiviral and antifungal therapies • Growth factors for individuals with grade 3 neutropenia • Palliative radiotherapy on non-targeted lesions	Prohibited concomitant medication: • Vaccination with live or live attenuated vaccines within 4 weeks of signing the ICF • Anti-lymphoma therapy (e.g. chemotherapy, radiotherapy or experimental therapy) • Corticosteroid that exceeded a total dose of 10 mg prednisolone or equivalent administered for more than ten days
Primary outcome	Overall response rates by Lugano criteria, assessed by IRC	
Key secondary outcomes	• DOR, CR, DOCR, PFS, TTR determined by Lugano criteria • ORR, CR, PFS, DOR, DOCR, TTR determined by LYRIC criteria • OS • TTNT • Rate of MRD negativity • Safety • PK parameters • FACT-Lym and EQ-5D-3L	
Duration of study and follow-up	The treatment period continued until disease progression unless the patient fulfilled one of the discontinuation criteria with the trial running for a maximum of five years after the last patients first dose. The final CSR will be available for regulatory purposes for the pivotal iNHL expansion cohort and is expected Q2 2028. The final CSR for the FL optimisation cohort is expected Q3 2029. The data cut presented in this submission is [REDACTED]	

ALT, alanine transaminase; ASCT, autologous stem cell transplantation; AST, aspartate transaminase; CAR-T, chimeric antigen receptor T-cell; CR, complete response; CRS, cytokine release syndrome; CTLS, clinical tumour lysis syndrome; DOCR, duration of complete response; DOR, duration of response; DLBCL, diffuse large B-cell lymphoma; ECOG, eastern cooperative oncology group; FL, follicular lymphoma; HGBCL, high-grade B-cell lymphoma; HSCT, hematopoietic stem cell transplantation; ICF, informed consent form; IRC, independent review committee; LYRIC, Lymphoma Response to Immunomodulatory Therapy Criteria; MRD, minimal residual disease; MRI, magnetic resonance imaging; ORR, overall response rate; OS, overall survival; PFS, progression free survival; PK, pharmacokinetic; PMBCL, primary mediastinal B-cell lymphoma; SC, subcutaneous; TTR, time to complete response; TTR, time to response; ULN, upper limit of normal; WHO, World Health Organisation

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2.5.1 Patient Characteristics

The baseline characteristics for the 4L+ FL cohort are presented in Table 11. In total, 65.4% (n = 53) of patients in the 4L+ FL cohort were male and 63.0% (n = 51) were white. Race was not reported in 33.3% (n = 27) patients. Mild to moderate renal impairment was reported in over half of the patients (66.7%, 54 patients). Normal hepatic function was reported in the majority of patients (80.2%, 65 patients).

2.5.2 Baseline disease characteristics

Over half of patients in the 4L+ FL subgroup had Grade 2 FL (45 patients, 55.6%). A further 27 patients (33.3%) had Grade 3A FL and 9 patients (11.1%) had Grade 1 FL (Table 11). The majority of this subgroup had a FLIPI score of ≥ 3 (57 patients, 70.4%), with 13 patients (16.0%) and 11 patients (13.6%) having FLIPI scores of 2 and 0-1, respectively. Over half of the 4L+ patients were double refractory to anti-CD20 and alkylating agents at any treatment line (60 patients, 74.1%).

Table 11. Patient Baseline Demographic and Disease Characteristics, 4L+ cohort

	Expansion Part
	4L+ FL (N = 81)
Age at informed consent (years)	
Mean (SD)	64.8 (11.06)
Median	66.0
Min, Max	39, 84
Sex (at birth)	
Male	53 (65.4%)
Female	28 (34.6%)
Race	
White	51 (63.0%)
Black or African American	0
Asian	3 (3.7%)
Other	0
Not reported	27 (33.3%)
Ethnicity	
Hispanic or Latino	0

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Not Hispanic or Latino	12 (14.8%)
Not reported	1 (1.2%)
BMI (kg/m²) category at baseline	
<18.5	1 (1.2%)
18.5 ≤ 25.0	39 (48.1%)
25 ≤ 30	27 (33.3%)
≥ 30.0	14 (17.3%)
ECOG Performance status	
0	40 (49.4%)
1	38 (46.9%)
2	3 (3.7%)
Baseline renal function classification by Cockcroft- Gault method (CrCl)[mL/min]	
Normal (≥ 90)	27 (33.3%)
Mildly impaired (60 ≤ 90)	38 (46.9%)
Moderately impaired (30 ≤ 60)	16 (19.8%)
Severe impairment	0
Baseline hepatic function per NCI criteria⁵⁹	
Normal	65 (80.2%)
Mild Dysfunction	16 (19.8%)
Moderate dysfunction	0
Severe dysfunction	0
Disease type at trial entry	
FL Grade 1-3A	81 (100%)
Histological grade	
1	9 (11.1%)
2	45 (55.6%)
3A	27 (33.3%)
Not applicable	0
Median time for initial dose to first dose ^a (years)	0
FLIPI	
0-1	11 (13.6%)
2	13 (16.0%)
≥3	57 (70.4%)
Unknown	0
Not applicable	0

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POD24	
Progression, transformation or relapse within 24 months of initiating first-line immunochemotherapy	30 (37.0%)
Double refractory to anti-CD20 and alkylating agents, regardless of two treatments being in the same or different treatment lines	60 (74.1%)
Bone Marrow Involvement	
Bone marrow involvement at baseline by investigator	26 (32.1)

Data cut [REDACTED], assessed by independent review committee

“-“ not reported

a. Time from diagnosis of disease recorded at time of study entry.

BMI, body mass index; DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern cooperative oncology group; FL, follicular lymphoma; FLIPI, follicular lymphoma international prognostic index; MZL, mantle cell lymphoma; NCI, National Cancer Institute; SLL, small lymphocytic lymphoma; POD24, progression of disease 24 months.

2.5.2.1 Clinical opinion on patient characteristics

During interviews conducted by AbbVie in 2024, UK clinical experts provided feedback on the generalisability of the full FL1-3A 3L+ EPCORE NHL-1 trial population.

Generally, UK clinicians stated that the baseline characteristics of patients in the EPCORE NHL-1 trial aligned with those of patients in UK clinical practice. Some noted that the overall fitness (e.g. comorbidity profile) of patients is reduced compared with standard trial populations, presenting with high risk features that are typical in real world populations.⁵ As discussed in Section 2.15, it is therefore, anticipated that the results observed will closely parallel the responses expected in clinical practice.

2.5.2.2 Prior medication and procedures

The patient population enrolled in the iNHL cohort represents a heavily pre-treated, chemo-refractory and high-risk FL population. All 81 patients in the 4L+ subgroup had received prior chemotherapy with combined anti-CD20 and alkylating agents. Of the [REDACTED] who underwent ASCT, [REDACTED] within 12 months of receiving ASCT. Forty-one (50.6%) patients in the 4L+ subgroup had received 3 prior lines of therapy and 40 (49.4%) patients had received 4 or more prior lines of therapy.

2.5.2.3 Patient disposition

As of the [REDACTED] DCO, [REDACTED] patients ([REDACTED]%) of patients within the 4L+ FL cohort were receiving ongoing trial treatment, with the main reasons for study treatment discontinuation being progressive disease (n = [REDACTED], [REDACTED]%) and adverse events (n = [REDACTED], [REDACTED]%). Over half of the 4L+ FL cohort remained in the EPCORE NHL-1 trial (n = [REDACTED], [REDACTED]%; Table 12). The median follow-up time was [REDACTED] months as of [REDACTED].

Table 12. Patient disposition – 4L+ FL

	4L+ FL (N = 81)
Treated patients	
Ongoing trial treatment	[REDACTED]
Discontinued treatment	[REDACTED]
Primary reason for study treatment discontinuation	
Progressive disease	[REDACTED]
Clinical Progression	[REDACTED]
Disease progression according to response criteria	[REDACTED]
Adverse event	[REDACTED]
Withdrawal of subject	[REDACTED]
Decision to proceed with transplant	[REDACTED]
Other	[REDACTED]
Patients remaining on trial	[REDACTED]
Discontinued from trial	[REDACTED]
Primary reason for trial discontinuation	
Death	[REDACTED]
Lost to follow-up	1
Subject withdrew consent from trial.	[REDACTED]

Data cut [REDACTED]

a. Progressive disease includes both clinical progression and document radiographic disease progression
FL, follicular lymphoma

2.6 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

2.6.1 Trial populations

A total of 155 patients, 128 with FL and 27 with other iNHL subtypes were included in the iNHL cohort and treated with epcoritamab. Of the 128 FL patients with two or more prior lines of therapy (3L+), 81 patients were at 4L+.

The definitions used for the analysis sets are summarised in Table 13. All efficacy analysis were performed on the full analysis set (FAS) (n = 155), the population of patients who received at least one dose of epcoritamab. The data presented within the main Company Submission are for the 4L+ FL (n = 81) population.

Table 13. Analysis sets used for the outcomes in EPCORE NHL-1 (iNHL cohort)

Enrolled patients	All patients who signed the consent form
Full Analysis Set (FAS)	All enrolled patients who have been exposed to at least one dose of epcoritamab
Modified Full analysis set (mFAS)	The initial 100 consecutively treated grade 1-3A FL patients. Of these 100 patients, all responders would have 13 month follow up from their initial response date or discontinued earlier by the planned cutoff date
Safety analysis set (SAF)	All enrolled patients who have been subjected to at least one dose of epcoritamab
Response evaluable set (RES)	All patients in the FAS with measurable disease at baseline and have either died within 60 days of the first dose, or have at least 1 post-baseline disease assessment
Per-protocol Analysis set (PP)	All patients in the FAS with measurable disease at baseline and do not have a protocol deviation of note.
Pharmacokinetic Analysis set	All patients in the FAS collected with at least one evaluable PK sample
Immunogenicity Analysis set (IAS)	All patients in the FAS with an evaluable baseline anti-drug antibody sample and at least one ADA sample
PRO Analysis set	All patients in the FAS with a baseline and at least one post-baseline PRO score

FL, follicular lymphoma; PRO, patient reported outcome

2.6.2 Statistical analyses

The statistical analyses used in EPCORE NHL-1, alongside sample size calculations and methods for handling missing data are presented in Table 14.

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Table 14. Summary of statistical analyses in EPCORE NHL-1

Hypothesis objective	Expansion part The expansion part of the trial was carried out in two stages within the three cohorts. 33 patients with FL grade 1-3A were enrolled in stage 1, If futility criteria were met, no further expansion would have continued: Null Hypothesis: H_0: ORR for FL 1-3A is at most 50% (no more than 15 responders out of 30). Alternative hypothesis: ORR is at least 65%. As futility criteria were not met, an additional 95 patients with FL grades 1-3A were enrolled to stage 2, along with up to 30 patients with other iNHL (MZL, SLL), with up to 158 patients being enrolled in the iNHL cohort. No formal statistical hypotheses were formulated for Stage 2 of the trial.
Statistical Analysis	For categorical or ordinal variables, frequencies, and percentages of patients in each category are displayed in contingency tables. The denominator is determined by the analysis set used for the summary. Percentages provided in the contingency tables are rounded to the first decimal place. For continuous variables, descriptive statistics include number of non-missing values (n), mean, standard deviation, median, minimum and maximum values. In addition, 25th percentile and 75th percentile may also be provided. Time to event variables were analysed using Kaplan-Meier (KM) estimates (median time, first and third quartiles) with the number and percentage of patients with event or censoring along with censoring reasons reported. If specified, 95% confidence intervals are provided using the Brookmeyer and Crowley method with log-log transformation. All main efficacy analyses are based on FAS and mFAS, with sensitivity analyses for primary analysis in the PP and RES.
Sample size and power calculation	Expansion part Assuming a non-evaluable rate of 10% a sample size of 33 was estimated to provide approximately 90% power to reject the null hypothesis with a two-sided significance level of 0.05. The probability of futility at the end of Stage 1 is approximately 57% under the null hypothesis and 6.5% under the alternative hypothesis.
Data management and patient withdrawals	Expansion part Primary endpoint analysis: IRC-assessment ORR determined by Lugano criteria ORR was defined as the proportion of patients who achieved BOR of complete response or partial response. The primary analysis was conducted approximately 9 months after the last patients first dose of epcoritamab. ORR disease control rate and the corresponding 95% CI are provided for the FL 1-3A, other subtype and overall iNHL control. Secondary endpoint Analysis: The secondary endpoint of ORR was assessed by LYRIC criteria with corresponding 95% exact CI.

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	Time to response (TTR): TTR defined as time from Day 1 of Cycle 1 to the first documentation of objective tumour response (PR or better). TR assessed by Lugano was summarised by descriptive statistics. Duration of response (DOR): DOR was defined as the time from the first documentation of response (CR or PR) to the date of first report of PD or death, whichever occurs first. This response was assessed by both Lugano and LYRIC criteria. DOR by IRC per Lugano criteria was summarised with descriptive statistics, as well as median, first and third quantile along with two-sided 95% CI. DOR by IRC per Lugano criteria, estimated using the KM product-limit method was displayed graphically in FAs. A primary definition of DOR accounted for subsequent anti-lymphoma therapy and censors DOR at the last adequate tumour assessment on or prior to the date of subsequent lymphoma therapy. The secondary definition of DOR did not account for subsequent anti-lymphoma therapy. Complete response rate, time to complete response and duration of complete response rate: Complete response rate was defined as the proportion of patients with BOR of CR. Duration of complete response was defined as the time from the first documentation of CR to the data of PD or death whichever comes earlier. DOCR was derived for patients reaching CR. DOR by IRC per Lugano criteria was summarised by the number of events, minimum, maximum, median, first and third quantile, and two-sided 95% CI computed based on log-log transformation. Time to CR (TTCR) TTCR is defined as the time from Day 1 of Cycle 1 to the first documentation of objective tumour response of CR. TTCR was derived for patients who achieve the best response of CR and summarised with descriptive statistics. Progression-free survival Progression free survival (PFS) was defined as the time from Day 1 of Cycle 1 to the date of PD or death, due to any cause, whichever occurs earlier. Date of PD was defined as the earliest date of documentation progression after which there was no more PR or CR assessment. PFS was determined as for DOR described above. Two definitions of PFS were used in the analysis. The primary definition of PFS accounts for a subsequent anti-lymphoma therapy and patients who are alive without documented disease progression will be censored at the last adequate tumour assessment date or prior to the date of subsequent anti-lymphoma therapy. The subsequent anti-lymphoma therapies for PFS censoring in general consists of systemic anti-lymphoma therapy and radiation of any target lesion. Overall Survival Overall survival (OS) was defined as the time from Day 1 of Cycle 1 to death from any cause. If a patient is not known to have died, then OS was censored at the last date the patient was known to be alive. Survival status was assessed at least every 3 months after the last administration of epcoritamab and continued until the patient died or withdrew from the study. Optimisation part Primary end point analysis

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	Rate of ≥ 2 grade CRS event and all grade CRS event from first dose through 7 days of administration of the second dose Second endpoints Rate of ≥ 2 grade CRS event and all grade CRS events following first full dose Rate of ≥ 2 grade CRS events and all grade CRS events overall Safety and AEs. ORR, CR, DOR, DOCR, PFS, OS and TTNT as defined above.

BOR, best overall responses; CR, complete response; CRS, cytokine release syndrome; DoCR, duration of complete response; DOR, duration of response; FAS, full analysis set; FL, follicular lymphoma; iNHL, indolent non-hodgkin's lymphoma; IRC, independent review committee; KM, Kaplan-Meier; LYRIC, Lymphoma Response to Immunomodulatory Therapy Criteria; MZL, marginal zone lymphoma; ORR, overall response rate; OS, overall survival; PD, progressed disease; PFS, progression free survival; PR, partial response; SLL, small lymphocytic lymphoma; TTNT, time to next treatment; TTR, time to response.

2.6.2.1 Impact of Omicron wave of the COVID-19 pandemic on the dose expansion part of the EPCORE NHL-1 trial

As the EPCORE NHL-1 trial took place throughout the Omicron wave of the COVID-19 pandemic, patients in the trial were susceptible to infection with the Omicron variant – a highly infectious variant of COVID-19 with immune escape properties allowing it to reinfect previously infected or vaccinated patients.⁶⁰ As a result, excess mortality was observed in the trial that can be attributed to COVID-19, an external factor to the monitoring of deaths attributed to FL's natural history and epcoritamab efficacy. As an international trial, EPCORE NHL-1 was exposed to variation in COVID-19 prevalence and the management strategies adopted by different countries. As a result, a higher number of deaths due to COVID-19 were observed in different countries during EPCORE NHL-1, based on the effectiveness of these local management protocols and prevalence, which were beyond the control of the trial investigators.

It is important to view the survival data from the pivotal study in the context that the UK is no longer experiencing high numbers of COVID-19 infections, and the composite impact of immunity and vaccination status, particularly for immunocompromised patients, means the risk of death from COVID-19 remains low and, in the future, will continue to decline. Given that excess COVID-19 mortality may have been more pronounced during earlier, higher-risk waves with lower vaccine uptake, it is crucial to adjust for this excess mortality to characterise the true therapeutic benefit of epcoritamab in the current UK setting. This excess mortality predominantly related to the Omicron wave was clinically adjudicated in a thorough review of each mortality event in the trial, to identify cases where COVID-19 was the cause of death with certainty.

Based on the clinical adjudication and review of the trial data and site investigator reports, a total of ■ patient deaths were attributable to COVID-19 within the 4L+ population, of which ■ occurred during the Omicron wave of the pandemic. Of the ■ deaths attributed to COVID-19, ■ had occurred in patients in a CR at the time of their death. Such patients with a CR would typically have significantly extended OS

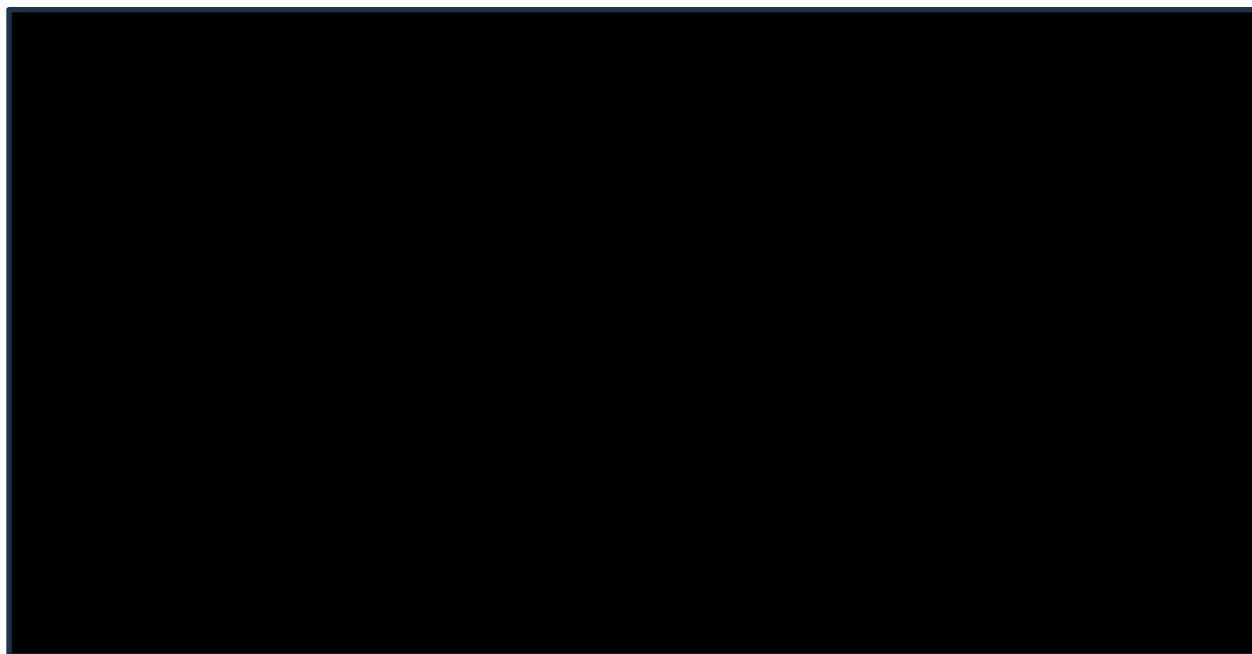
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compared with patients who achieve a partial response or no response (Figure 30; Section 3.3.2.5.1.1).

The inclusion of these deaths within the survival analysis produces inappropriately pessimistic estimates of long-term outcomes for patients treated with epcoritamab, given the deaths would likely not have occurred had the trial not taken place during the Omicron phase of the pandemic. As such, and aligned with the conclusions described in the publication by Linton et al 2024,⁶¹ COVID-19 deaths are censored in the survival outcomes (OS, PFS and TTD) presented in Section 2.8 and the MAIC analysis performed in Section 2.12 to best reflect the current real-world situation.

For illustrative purposes, the OS using both the unmodified and modified analyses are presented below (Figure 7). Here, the impact of the Omicron variant on patient mortality can clearly be seen between months 12 and 15 of follow-up.²

Figure 7: Kaplan-Meier curves of epcoritamab OS data demonstrating the impact of the Omicron wave of the COVID-19 pandemic



Data cut [REDACTED]

The dose optimisation part of the EPCORE NHL-1 trial (presented in Section 2.14) took place outside of the Omicron wave of the COVID-19 pandemic (initiating in October

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2022), and as such is more representative of the current clinical setting for epcoritamab use, without the confounding nature of the COVID-19 pandemic. As of the 08 Jan 2024 data cut off, no COVID-19 associated deaths were reported in this cohort (Table 32). As such, when considering the survival data from the Dose Optimisation part of the study, great care should be made to consider anticipated patient outcomes in current clinical practice where the COVID-19 pandemic, and in particular the Omicron variant, is no longer prevalent.

2.7 Critical appraisal of the relevancy of clinical effectiveness evidence

The clinical effectiveness evidence provided in this submission is derived from the EPCORE NHL-1 trial, conducted within the requirements of the regulatory bodies. The quality assessment of this trial is provided in Table 15. A full quality assessment of the trial using the Down's and Black checklist is provided in the data extraction file, included in the Clinical SLR report in Appendix B.⁶²

Table 15. Quality assessment results for EPCORE NHL-1

Author, Year	AbbVie Clinical Study Report, 2024
Trial acronym	EPCORE NHL-1
What is the study design of this trial?	Single armed
Was the study a prospective or a retrospective study?	Prospective
In case of a case control study, were the groups similar at the outset of the study in terms of prognostic factors	N/A
Was the intervention used appropriately?	Yes, the dosing regimen in the trial reflects the expected dosing schedule for epcoritamab in its SmPC.
Were the outcomes measured in the study reliable?	Yes, the key outcomes of the trial are objective measures such as survival. Other key results such as response rates were determined by both independent review committees and the investigator.
Were the outcomes measured in the study valid?	Yes, the outcomes of the trial align with the decision problem and are clinically relevant measures to demonstrate the benefits of epcoritamab.

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Was the statistical analysis conducted appropriately in the study?	Yes, the study was powered to provide statistically robust results
Was the quality of the reporting appropriate in the study?	Yes, all outcomes are reported in the clinical study report
Can the study results be generalised to routine practice?	Yes, more details are provided in Section 2.15.2

2.8 Clinical effectiveness results of the relevant studies

2.8.1 Overview of the clinical effectiveness results

This part of the clinical evidence will focus on the 4L+ FL cohort (n = 81), the appraisal population. The data presented herein have been adjusted to censor deaths related to the COVID-19 pandemic, as outlined in Section 2.6.2.1. Non-COVID adjusted data and further evidence presented to give context on the efficacy and safety of epcoritamab in the full trial population for FL (n = 128) are presented in Appendix M. Additional data to further support the efficacy from the ongoing optimisation part of the EPCORE-NHL1 trial are provided for the C1-Opt 4L+ cohort in Section 2.14 and for the C1-Opt 3L+ cohort in Appendix M. An overview of the clinical effectiveness of epcoritamab in the 4L+ FL cohort is presented in Table 16.

Table 16. Overview of clinical effectiveness, 4L+ cohort

	Expansion Part
	4L+ (n = 81)
ORR	██████
(95% CI) ^a	████████
CR	██████
(95% CI) ^a	████████
DOR (months) all responders	
Number of responders	█
Min, Max ^b	██████
Median (95% CI) ^c	████████
DOCR (months)	
Number of responders	█
Min, Max	██████
Median (95% CI) ^c	████████
PFS (months)	
Number of events	██████
Min, Max ^b	██████
Median (95% CI) ^c	████████
OS (months)	
Number of events	██████
Number censored	██████
Min, Max	██████
Median (95% CI) ^c	████████

Data cut ██████, assessed by independent review committee

a. Based on the Clopper and Pearson method. b. Symbol '+' indicates a censored value. c. Based on Kaplan-Meier estimates. CI, confidence interval; CR, complete response rate; DoCR, duration of complete response; DOR, duration of response; FL, follicular lymphoma; IA, investigators assessment; ORR, overall response rate; PFS, progression free survival.

2.8.2 Primary endpoint of EPCORE NHL-1

The primary outcome from the Expansion Part of the EPCORE NHL-1 trial was ORR, assessed by an IRC using the Lugano criteria. A summary of the key clinical outcomes of the EPCORE NHL-1 trial for the 4L+ FL cohort are presented in Table 17. Response was observed in █% of patients (n = █), of which █% (█ patients) achieved a CR and █% (█ patients) achieved a partial response. Stable disease was observed in █ patients (█%).

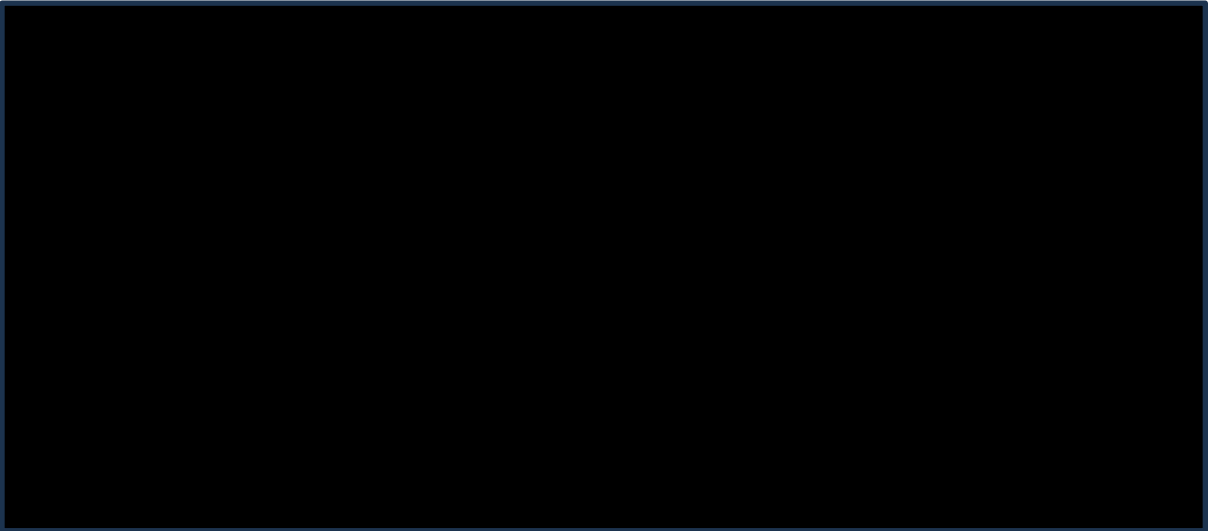
Table 17. Best Overall Response, 4L+ cohort

	Expansion part
	4L+ FL (N = 81)
Overall response Rate (ORR) ^a	████
(95% CI) ^b	██████
Complete response rate (CRR)	████
(95% CI) ^b	██████
Partial response rate (PRR)	████
(95% CI) ^b	██████
Best overall response	
Complete response	████
Partial response	████
Stable disease	████
Progressive disease	████
Not Evaluable	████

Data cut █, assessed by independent review committee ± Data cut 8 January 2024, assessed by investigator
a. CR + PR. Includes patients who had a PR or CR after an assessment of PD or indeterminate response (i.e. Pseudoprogression).
b. Based on the Clopper and Pearson method.
CRR, complete response rate; ORR, overall response rate; PRR, partial response rate

A waterfall plot of best reduction in sum of the product of the diameters (SPD) by IRC assessment determined by Lugano criteria is provided for patients with 4L+ FL 1-3A in Figure 8.

Figure 8. Waterfall plot of best reduction in SPD based on IRC assessment per Lugano criteria – 4L+ cohort



Asterisks indicate an increase of more than 100% in sum of product of perpendicular diameters. Only subjects with baseline and at least one valid post-baseline tumour assessment are included in the analysis.
CR, complete response; PD, disease progression; PR, partial response; SD, stable disease; SPD, sum of the products of the longest perpendicular diameters

2.8.3 Secondary Endpoints

2.8.3.1 Duration of Response (DOR) Determined by Lugano Criteria

DOR was defined as the time from the first documentation of response (CR or PR) to the date of death or PD (where PD is defined as the date of earliest disease progression, after which there are no more PR or CR assessments), whichever comes first. The DOR (primary definition) based on IRC assessment determined by Lugano criteria for the 4L+ FL cohort is presented in Table 18.

The median DOR was █ (95% CI: █, █) over a median of █ months follow-up. At 12 and 18 months, █% and █% of patients remained in response, respectively. A KM plot for DOR based on ICR assessment for the 4L+ FL cohort patients is presented in Figure 9.

Table 18. Duration of response, 4L+ cohort

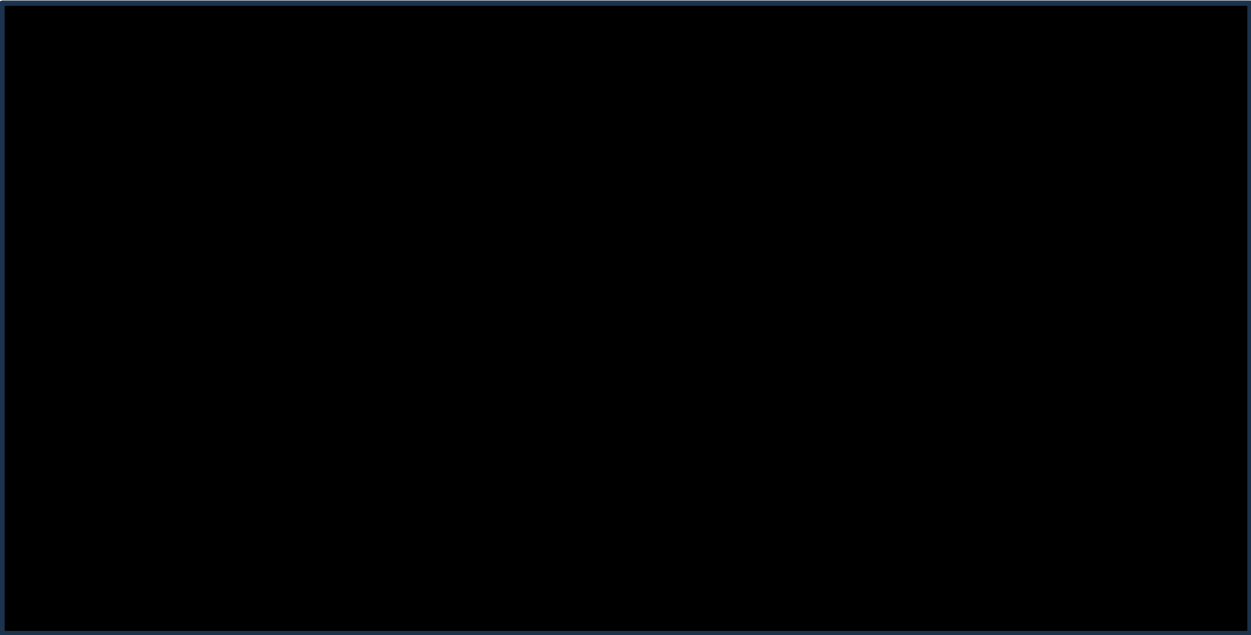
	Expansion Part
	4L+ FL (N = 81)
All responders (PR or CR)	
Number of Responders	████████
Number of Events	████████
Number of Censored	████████
Reason for Censoring	
Clinical cutoff	████████
New anti-lymphoma therapy	████████
Lost to follow-up	1
Subject withdrew consent	████████
PD (or death) after ≥ 2 consecutive missed tumour assessment	████████
Other	████████
DOR	
Median follow-up (95% CI) ^a	████████
Median DOR (95% CI) ^b	████████
Estimated percentages of patients remaining in response (95% CI)^b	
6-month	████████
12-month	████████
18-month	████████
24-month	████████
30-month	████████
36-month	████████

Data cut ██████████, assessed by independent review committee

a. Based on reverse Kaplan-Meier estimates. b. Based on Kaplan-Meier

CI, confidence interval; CR, complete response; DOR, duration of response; FAS, full analysis set; IRC, independent review committee; max, maximum; min, minimum; NR, not reached; PR, partial response

Figure 9. Kaplan-Meier Plot of Duration of Response based on IRC Assessment, Lugano Criteria, 4L+ FL



Data cut off [REDACTED].
CI, confidence interval; FAS, full analysis set; NR, not reached

2.8.3.2 Duration of Complete Response (DOCR) determined by Lugano Criteria, 4L+ Cohort

The median (95% CI) DOCR for patients with 4L+ FL was [REDACTED] ([REDACTED], [REDACTED]) with a median follow-up time of [REDACTED] months ([REDACTED], [REDACTED]). The percentage of 4L+ patients remaining in CR at 18 and 36 months was [REDACTED]% and [REDACTED]%, respectively, as shown in Table 19.

Table 19. Duration of Complete Response, 4L+ cohort

	Expansion Part
	4L+ FL (N = 81)
Complete responders (CR)	
Number of Responders	[REDACTED]
Number of Events	[REDACTED]
Number of Censored	[REDACTED]
Reason for Censoring	
Clinical cutoff	[REDACTED]
New anti-lymphoma therapy	[REDACTED]

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Lost to follow-up	I
Subject withdrew consent	
PD (or death) after ≥ 2 consecutive missed tumour assessment	
Other	
DOCR	
Median follow-up (95% CI) ^a	
Median DOCR (95% CI) ^b	
Estimated percentages of patients remaining in response (95% CI)^b	
6-month	
12-month	
18-month	
24-month	
30-month	
36-month	

Data cut [REDACTED], assessed by independent review committee
a. Based on reverse Kaplan-Meier estimate. b. Based on Kaplan-Meier estimate
CI, confidence interval; NR, not reached; PD, progressed disease

2.8.3.3 Progression-free survival (PFS), 4L+ cohort

PFS based on IRC assessment (by primary definition) for the 4L+ FL cohort is presented in Table 20 and Figure 10. In total, [REDACTED]% (n = [REDACTED]) experienced a progression or mortality event with a median PFS of [REDACTED] months (95% CI: [REDACTED], [REDACTED]). The estimated percentage of patients remaining progression-free at 18 and 36 months was [REDACTED]% and [REDACTED]%, respectively.

Table 20. Progression Free Survival, 4L+ Cohort

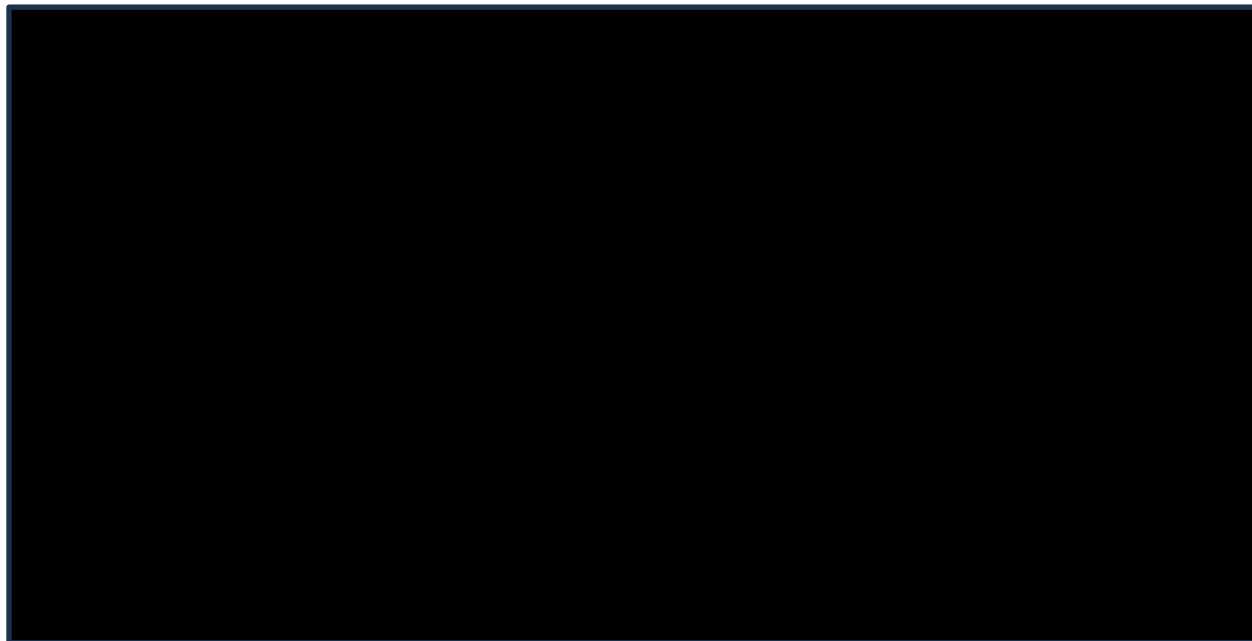
	Expansion Part
	4L+ FL (N = 81)
Number of Events	████████
Number of Censored	████████
Reason for censoring	
Clinical Cutoff	████████
New anti-lymphoma therapy	████████
Lost to follow-up	█
Participant withdrew consent	██████
PD (or death) after ≥ 2 consecutive missed tumour events	██████
No baseline assessments	█
No post-baseline assessments	██████
Other	██████
PFS (months)	
Median follow-up (95%CI) ^a	██████████
Median PFS (95% CI) ^b	██████████
Estimated percentage of patients remaining progression-free (95% CI)^b	
6-month	██████████
12-month	██████████
18-month	██████████
24-month	██████████
30-month	██████████
36-month	██████████

Data cut ██████████, assessed by independent review committee

“-“ Not reported

a. Based on reverse Kaplan-Meier estimate. b. Based on Kaplan-Meier estimate
CI, confidence interval, NR, not reached

Figure 10. Kaplan-Meier Plot of Progression- Free Survival based on IRC Assessment, Lugano Criteria, Primary definition, 4L+ FL cohort



Data cut off [REDACTED], assessed by independent review committee
CI, confidence interval; FL, follicular lymphoma; NR, not reached

2.8.3.4 Overall Survival (OS), 4L+ FL cohort

By the [REDACTED] data cut off, [REDACTED] patients ([REDACTED]%) in the 4L+ cohort had died after a median follow up time of [REDACTED] months, at which point [REDACTED]. The estimated percentage of 4L+ patients alive at 18 and 36 months was [REDACTED]% and [REDACTED]% months, respectively, as shown in Table 21.

Table 21. Overall Survival, 4L+ FL cohort

	Expansion Part
	4L+ FL (N = 81)
Number of events	
Number of Censored	
OS (months)	
Median follow-up (95%CI) ^a	
Median OS (95% CI) ^b	
Estimated percentage of patients remaining alive (95% CI) ^b	
6-month	
12-month	
18-month	
24-month	
30-month	
36-month	

Data cut [REDACTED], assessed by independent review committee
a. Based on reverse Kaplan-Meier estimate. b. Based on Kaplan-Meier estimate
CI, confidence interval; NR, not reached

Figure 11. Kaplan-Meier Plot of Overall Survival, 4L+ FL Cohort



Data cut off [REDACTED], assessed by independent review committee
CI, confidence interval; FAS, full analysis set; NR, not reported.

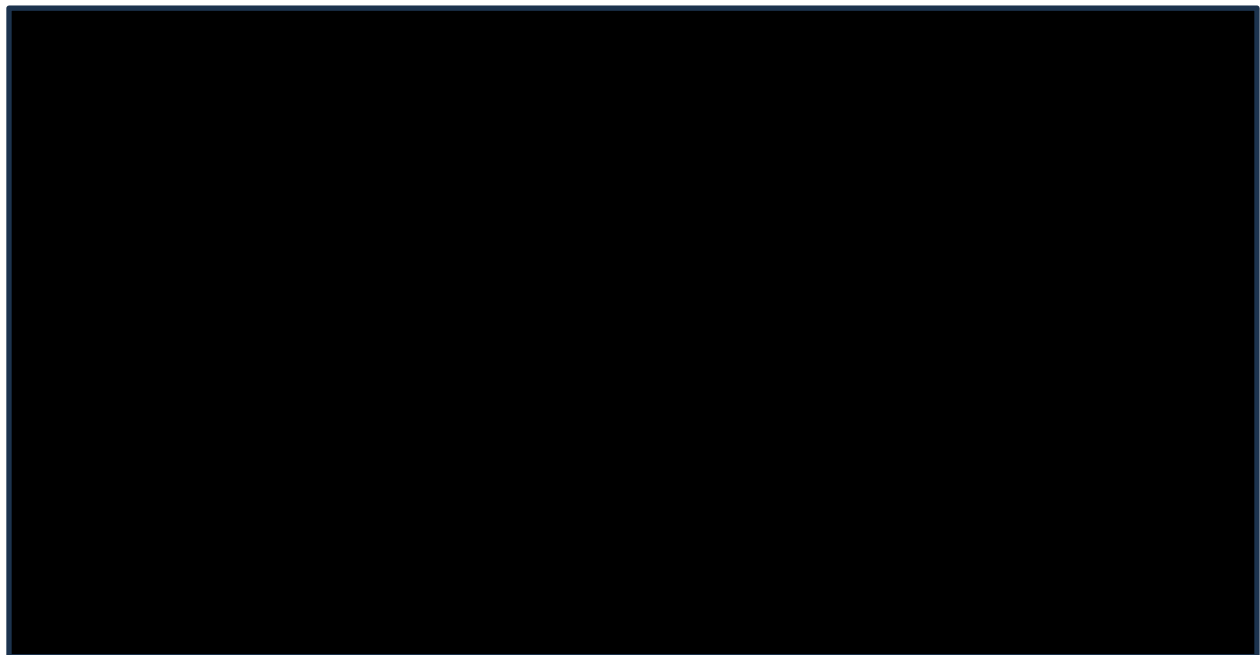
2.8.4 Patient reported outcomes

2.8.4.1 Functional Assessment of Cancer Therapy- Lymphoma subscale (FACT-LymS), 4L+ FL Cohort

The FACT-LymS was developed to measure health-related quality of life (HRQoL) for patients with NHL. The FACT-LymS consists of 15 statements for patients to respond to on an identical 5-point scale and takes physical, social and mental well-being into consideration. The results from the FACT-LymS are presented on a numerical scale, ranging from 0 to 168, with higher scores being indicative of a better quality of life.⁶³ COVID-modified analyses were not performed for patient-reported outcomes.

As of the [REDACTED] DCO, the HRQoL of the 4L+ FL cohort, as determined by FACT-LymS, was maintained throughout the trial, Figure 12.

Figure 12. Mean Change from Baseline in FACT-LymS, 4L+ FL cohort



Data cut [REDACTED]
Horizontal reference line indicates minimum important difference (MID = range: 5.5-11)
FACT-Lym, functional assessment of cancer therapy – lymphoma; FL, follicular lymphoma.

2.8.4.2 EuroQoL-5 dimensions-3 levels (EQ-5D-3L), 4L+ FL Cohort

Changes in HRQoL as evaluated by the EQ-5D-3L were included as an exploratory endpoint of EPCORE NHL-1.

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Improvements in HRQoL, as determined by EQ-5D utility score, were observed in the 4L+ FL cohort with scores improving from █ (SD: █) at baseline to █ (SD: █) at the end of treatment (Figure 13).

Figure 13. Mean change from baseline in EQ-5D-3L health utility score – 4L+ FL cohort



Data cut █
Note: Horizontal reference line indicates minimum important difference (MID=0.008)
FL, follicular lymphoma.

2.9 Subsequent treatments used in the relevant studies

A summary of the subsequent treatments is presented in Table 22. Of the 81 patients in the 4L+ cohort, █% (n = █) initiated a subsequent treatment, with a mean of █ subsequent treatments. Only █% (n = █) patients underwent allogeneic SCT. Subsequent systemic drug therapies were received by █% (n = █) of patients, with █% (n = █) and █% (n = █) receiving antineoplastic agents and rituximab respectively. Radiotherapy was received by █% of patients (n = █).

Table 22. Subsequent treatments, 4L+ cohort

	Expansion Part
	4L+ FL (N = 81)
Number of subsequent lines of anti-lymphoma therapy	
n	██████
Mean (SD)	██████
Median	██
Min, Max	██
1, n (%)	██████
2, n (%)	██████
3, n (%)	████
≥4, n (%)	██████
Subjects with any subsequent anti-lymphoma therapy, n (%)	██████
Subjects received subsequent new tumour directed surgery, n (%)	████
Subjects received subsequent radiotherapy, n (%)	██████
Subjects received subsequent stem cell transplant, n (%)	██████
ASCT	████
Allogeneic SCT	██████
Subjects received subsequent CAR-T, n (%)	██████
Subjects received subsequent systemic drug therapy, n (%)	██████
Antineoplastic agents	██████
Rituximab	██████
Cyclophosphamide	██████
Vincristine	██████
Lenalidomide	██████
Bendamustine	██████
Doxorubicin	██████
Gemcitabine	██████
Idelalisib	██████
Investigational antineoplastic drugs	██████
Polatuzumab vedotin	██████
Zilovetamab	██████
Amdizalisib	██████
Bleomycin	██████

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Carboplatin	████
Chlorambucil	████
Etoposide	████
Fludarabine	████
Golcadomide	████
Jnj 64264681	████
Methotrexate	████
Oxaliplatin	████
Paclitaxel	████
Safimaltib	████
Stp 938	████
Valemetostat	████
Zandelisib	████

Data are n (%) unless otherwise stated. Percentages calculated based on number of subjects in Full Analysis Set
Subjects are counted at most one time within each generic name, and at most one time per each ATC level
Subsequent therapy is administered after study-drug discontinuation
ASCT, autologous stem cell transplant; SCT, stem cell transplant; SD, standard deviation

2.9.1 Time to Next Lymphoma Therapy (TTNT)

TTNT was defined as time from cycle 1, day 1 (C1D1) to first recorded administration of subsequent anti-lymphoma therapy with curative intent or death, whichever came first.

TTNT events were reported in █████% (████ patients) of 4L+ cohort, Table 23. Median TTNT was █████ months (████, █████) with a median follow-up of █████ months (████, █████). The estimated percentages of patients not initiating subsequent treatment was reported as █████% and █████% at 18 and 36 months, respectively.

Table 23. Time to Next Anti-lymphoma Therapy, 4L+ cohort

	Expansion Part
	4L+ FL (N = 81)
Number of Events	████
Number of Censored ^a	████
TTNT (months)	
Median follow-up (95%CI) ^b	████████
Median TTNT (95% CI) ^c	████████
Estimate percentage of patients not initiating next line of therapy (95% CI)^b	
6-months	████████

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12-month	
18-month	
24-month	
30-month	
36-month	

Data cut [REDACTED], assessed by independent review committee

"-" Not reported

a. All data presented have not been adjusted for COVID-related mortality b. Based on reverse Kaplan-Meier estimate c. Based on Kaplan-Meier estimate

CI, confidence interval; NR, not reached; TTNT, time to next anti-lymphoma therapy

2.10 Subgroup analysis

There is no subgroup analysis available for the 4L+ FL cohort. The EPCORE NHL-1 trial was not statistically powered to detect significant differences between sub-groups within the 4L+ FL population.

2.11 Meta-Analysis

An indirect treatment comparison (ITC) was conducted to compare epcoritamab with treatments currently available in 4L+ care in England as presented in Section 2.12.

2.12 Indirect and mixed treatment comparisons

EPCORE NHL-1 was a single arm trial, and no head-to-head trials comparing epcoritamab to relevant comparators were identified during the clinical SLR (Section 2.1 and Appendix B). Therefore, an ITC, in the form of an unanchored matching-adjusted indirect comparison (MAIC), was conducted to inform the relative efficacy estimates for epcoritamab, utilising the COVID-modified data collected from the Dose Expansion cohort of EPCORE NHL-1, versus current 4L+ care in England for this appraisal.

2.12.1.1 Methodology: Data Source

The unanchored MAIC was conducted in line with the approach outlined in Signorovitch et al. (2012),⁵⁷ and considering the methods described in NICE DSU TSD 18.⁵⁸ A SLR was conducted to identify, extract and analyse the relevant clinical evidence for 4L+ therapies in R/R FL, in line with the target population for epcoritamab, in order to

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characterise the current efficacy and safety profiles of current 4L+ care received by this patient group (Appendix B). The studies identified by the SLR are presented in Table 24, alongside a report from the Haematological Malignancy Research Network (HMRN).⁵

Of the studies identified during the SLR, none were appropriate to estimate relative effects for patients treated with 4L+ care in England due to the inclusion of therapies that are not used in routine NHS clinical practice; therefore, using such data in comparative effectiveness assessments for alternative 4L+ treatments is likely to yield unrepresentative results. In particular, the patient population studied in the SCHOLAR-5⁶⁴ trial was considered not generalisable to the UK, with approximately 50% of patients at 4L+ having been administered experimental treatments that are not available on the NHS (such as CAR-Ts and bispecific antibodies). Further, SCHOLAR-5 considered transplant as a line of therapy (LOT), which applied to 20-25% of patients. This is incongruous with how LOT is defined in UK clinical practice and in the EPCORE NHL-1 trial, where transplant is not considered as a LOT. When evaluating the LEO cohort⁶⁵, patients were exclusively from the United States and only 6% were at 4L+. PFS was not reported as part of the ReCORD-FL⁶⁶ trial, and similarly the majority of patients were at an earlier LOT than the Decision Problem for this appraisal.

The Company are aware that the SCHOLAR-5 data were presented as a relevant source of data for current 4L+ care within TA894 (axicabtagene ciloleucel for treating relapsed or refractory follicular lymphoma); however, the EAG raised issues with its generalisability to UK clinical practice. Additionally, in TA894, Kite-Gilead had access to patient-level data from the SCHOLAR-5 study and were, to some degree, able to mitigate these concerns through removal of the DELTA cohort (trial patients with prior idelalisib [a treatment not reimbursed in England]) of SCHOLAR-5. This option was not available to AbbVie during this submission.

None of the studies identified during the SLR were appropriate for using in an ITC, either as a result of the inclusion of a non-UK generalisable patient population or the inclusion of treatment options which are not available in the UK (i.e. CAR-T, bispecific

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antibodies etc). Therefore, AbbVie engaged with the HMRN to identify the most appropriate data to inform the MAIC. A similar approach was taken during the NICE submissions for other treatments for FL in TA627¹⁷, TA604⁶⁷ and recently for MZL in TA1001⁶⁸.

Table 24. Studies reporting outcomes for current 4L+ care

Trial Name	SCHOLAR-5	ReCORD-FL	LEO Cohort	HMRN
Author, year	Ghione, 2023 ⁶⁹	Salles, 2022 ⁶⁶	Casulo, 2022 ⁶⁵	N/A, 2025 ⁵
Country/region	US and Europe (France, UK, Spain, Portugal)	US, Canada, UK, France, Germany, Spain	US	UK
Proportion of patients from UK sites	17%	Unknown	0%	100%
Patients at each LOT	3L+: 39% 4L+: 28% 5L+: 33%	3L+: 80% 4L+: 17% 5L+: 3%	3L+: 94% 4L+: 5% 5L+: 1%	4L+: 100% [†]
Accessibility to baseline characteristics?	Yes	Yes	Yes	Yes
Available outcomes	ORR, CR, PFS, OS	ORR, CR, EFS, OS	ORR, CR, PFS, OS	ORR, CR, PR, PFS, OS
PFS and OS KMs available?	Yes	No PFS data are available. Only OS and EFS data are presented.	Yes	Yes

[†] Analysis from the HMRN was run specifically on 4L+ FL in line with the submission population
CR, complete response; EFS, event-free survival; KM, Kaplan Meier; LOT, line of treatment; NA, not applicable; OS, overall survival; ORR, overall response rate; PFS, progression free survival; PR, partial response

COVID-modified data from the EPCORE NHL-1 trial were used in the ITC to remain consistent with the absence of COVID-associated deaths in the HMRN dataset (only a fraction of patients had been followed-up during the COVID-19 pandemic) and recognising that the UK is no longer experiencing high numbers of circulating COVID-19 infection (Section 2.6.2.1).

2.12.1.2 Methodology: HMRN

The HMRN is an ongoing population-based cohort consisting of data for UK patients with R/R FL. The HMRN region covers two adjacent UK cancer networks with a total population of 3.8 million⁵, and is considered generalisable to the UK population. The Company evidence submission for epcoritamab for treating relapsed or refractory follicular lymphoma patients after three or more systemic treatments

report generated as part of AbbVie's engagement with HMRN covered 4L+ patients, and was the only identified data source considered suitable for inclusion in the ITC.⁵ A brief summary of the HMRN dataset population and clinical outcomes reported can be found in Table 25.

Table 25. Overview of the HMRN dataset

Population and patient numbers	Adults with R/R FL initiating ≥4 th LOT (N=■)
Inclusion criteria	1. Follicular lymphoma diagnosis recorded via WHO ICD-O-3 code including 9579, 9690, 9695, 9698 2. Aged ≥18 years at diagnosis 3. Received ≥3 prior lines of treatment for FL
Reported outcomes	• OS - Time (in months) from initiation of therapy to death (any cause). Patients who did not die within the study observation period were censored on last known alive date (31st December 2023) • PFS - Time (in months) from initiation of therapy to the first event out of end of treatment if refractory, relapse or death (any cause). Patients who did not have an event within the study observation period were censored on last known alive date (31st December 2023). • TTD - Time (in months) from initiation of therapy to the discontinuation of therapy for any reason. Patients who were on treatment at their last date of follow up were censored. • ORR – Proportion of patients achieving CR or PR • CR – Proportion of patients achieving CR • PR - Proportion of patients achieving PR
Median follow-up	Median follow-up of ■ was recorded for patients receiving 4L+ therapy for FL. This estimate is calculated from the time from initiating treatment at 4L+ FL to the end of follow-up, censoring for deaths.

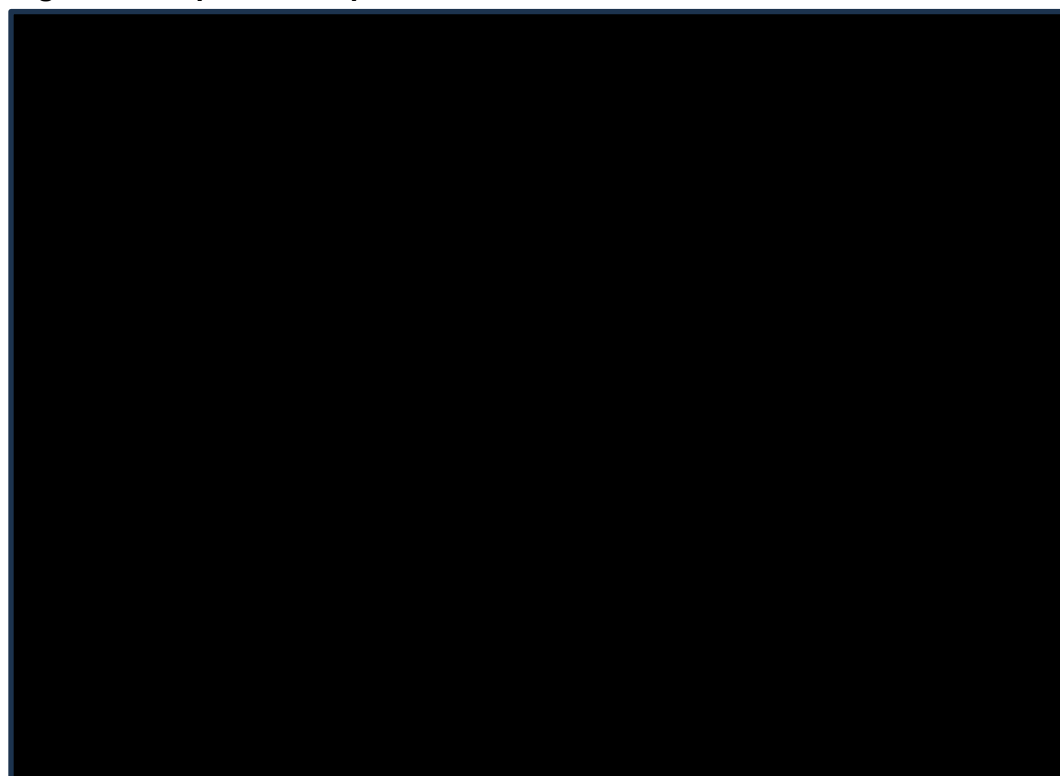
CR, complete response; FL, follicular lymphoma; NR, not reached; ORR, overall response rate; OS, overall survival; PFS, progression free survival; PR, partial response; TTD; time to discontinuation

As outlined in Section 1.3.6, there is no standardised treatment pathway for FL as patients move to later lines of treatment. A significant degree of variation is observed for 4L FL and beyond, where treatment options are particularly limited, and patients frequently receive repeat rituximab or chemo-based treatments. Therefore, in line with clinical feedback and the approach taken in TA894 and TA1001 (for MZL), the comparator in this appraisal is considered as a treatment basket of current 4L+ care, acknowledging that patient survival at 4L+ is consistently short with all existing treatment regimens.^{5,68,70,71}

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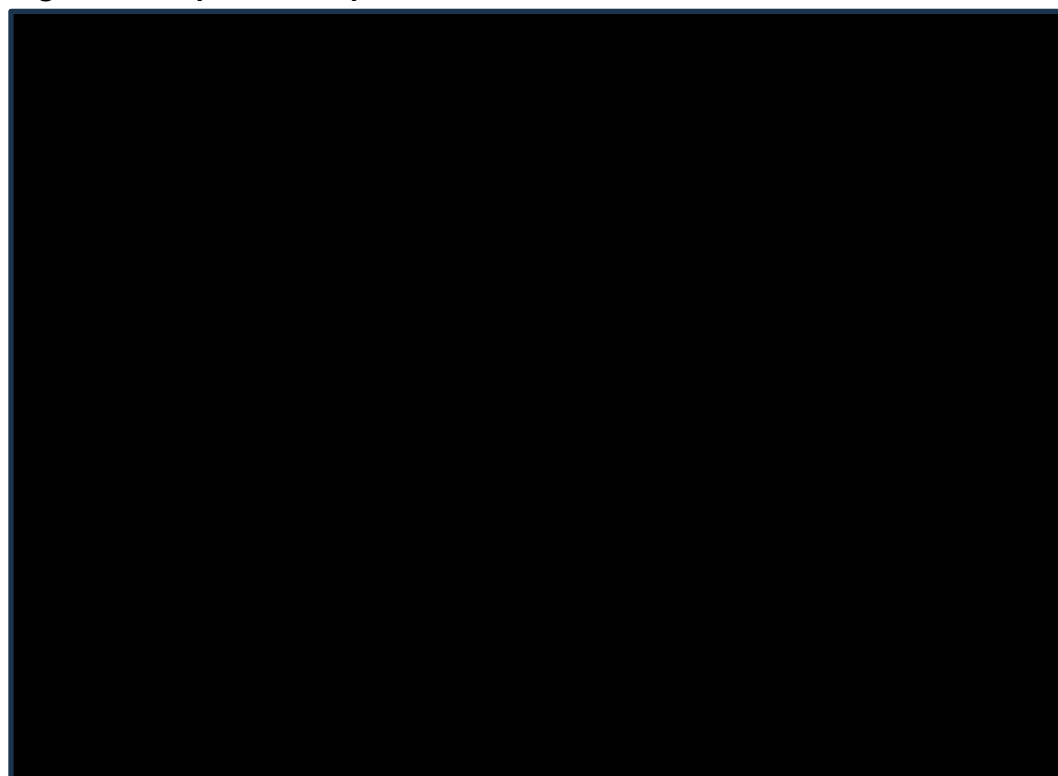
Outcomes for PFS and OS in patients with 4L+ R/R FL from the HMRN dataset are presented in Figure 14 and Figure 15. Consistent with the poor survival outcomes in patients at 4L+ R/R FL, median PFS in the HMRN dataset was [REDACTED] months, while median OS was [REDACTED] months.⁵ These outcomes were validated through engagement with clinical experts experienced in treating patients with FL across a range of centres around the UK.⁹

Figure 14. Kaplan-Meier plot of PFS from start of 4L+ in the HMRN dataset



HMRN, Haematological Malignancy Research Network; PFS, progression-free survival

Figure 15. Kaplan-Meier plot of OS from start of 4L+ in the HMRN dataset



HMRN, Haematological Malignancy Research Network; OS, overall survival

2.12.1.3 Methodology: MAIC

An unanchored MAIC was conducted following the recommendation of NICE guidance on population-adjusted indirect comparisons based on propensity score reweighting methods using individual patient data from EPCORE NHL-1 and aggregate data from the HMRN. Both MAICs and simulated treatment comparison (STC) aim to adjust for differences in population characteristics between data sources when head-to-head trials do not exist, but they utilise slightly different methodologies. In this case, the MAIC approach was preferred over STC for several key reasons, described below.

STC based parametric or semiparametric regression analyses rely on the number of events (not the number of patients) to determine the degrees of freedom; the lower the number of events, the lower the number of predictors that can be included in the model. As such, this method would not have been appropriate in this submission due to the small number of events recorded in the EPCORE NHL-1 study, which in turn would reduce the number of predictors that could be included in the model.

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MAICs are the preferred method of analysis when analysing time-to-event data for a single target comparator (or single RWE database) across multiple treatment outcomes, whereas STCs are more appropriate for analyses against multiple comparators. Further, conducting an STC on time-to-event outcomes requires a parametric distribution of the best fit and to assess whether the same distribution is applicable to both arms of the analysis. When considering prior NICE TAs, MAICs have been more frequently utilised and accepted in prior NICE appraisals of FL treatments, further supporting the methodological precedent for this analysis.

A key step in conducting a MAIC is the careful selection of patient characteristics for matching, ensuring that the analysis appropriately accounts for differences between trials to reduce the risk of bias. To achieve this, it is necessary to both establish which patient characteristics are known effect modifiers or prognostic variables (or can be plausibly considered as potential effect modifiers or prognostic variables) and determine whether these variables are imbalanced between the datasets being considered. The selection of characteristics for matching was made considering the availability of these characteristics in the comparator dataset, their inclusion in similar analyses presented in prior NICE TAs, and clinical opinion and empirical tests of whether these variables are predictive of survival or impact the efficacy in epcoritamab trial data.

MAICs have routinely been presented to and accepted by NICE as valid methodology across various appraisals of lymphoma therapies. The MAIC in this submission was conducted utilising learnings from previous NICE TAs: TA627, TA892 and TA894 and an overview of the approach taken in these appraisals is provided in Appendix K. In summary, following a review of TA627, TA892 and TA894, the unanchored MAIC presented within this submission considers the need to balance:

- i) reporting limitations of relevant prognostic variables or treatment effect modifiers in the published literature or data set,
- ii) the risk of overmatching and the impact on effective sample size,
- iii) the need to include as many potentially relevant adjustment factors as is feasible.

2.12.1.4 Summary

A summary of the key characteristics of the trials included in the ITC is presented in Table 26.

Table 26. Summary of ITC key characteristics

Dataset	Treatment	Trial Design	Indication of Study	Main patient criteria	Median Follow-up (months)
EPCORE NHL-1	Epcoritamab	Open labelled phase 1/2	R/R FL1-3A	3 ≥ prior LOT	
HMRN	Current 4L+ care in England	Observational, RWE	R/R FL at 4 LOT	3 ≥ prior LOT	

* Calculated as time from initiation of 4L+ FL treatment to the end of follow-up (reverse Kaplan-Meier method). Patients were followed-up until December 2023 and progression or death outcomes were not censored.

FL, follicular lymphoma; HMRN, Haematological Malignancy Research Network; ITC, indirect treatment comparison; LOT, line of treatment; R/R, relapsed/refractory; RWE, real-world evidence

2.12.2 Statistical methods

Epcoritamab individual-patient data from the 4L+ cohort (n=81) were used together with summary data from HMRN (n=■). Where only summary statistics are available, the Guyot methodology has been recommended by the NICE DSU (TSD 14)⁷² in order to re-create patient level data. Therefore, data from the HMRN 4L+ cohort were synthesised to generate event and censoring times for OS and PFS outcomes. These were extracted from the Kaplan-Meier graphs from the HMRN data via a two-step process:

1. The numerical value of the survival curves at dozens of time points were obtained through a graphical digitisation software, WebPlotDigitizer.
2. These values were used to create a “simulated” study population using the algorithm published by Guyot et al.⁷³ This simulated study population is a collection of event and censored times equal to the number of patients in the study population and creating a KM curve whose values are closest to that of the digitised data. These simulated patient-level data sets were then used in the ITC analyses.

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The EPCORE NHL-1 data were reweighted according to patient characteristics identified as the most relevant treatment effect modifiers and prognostic variables by empirical analyses, clinical experts and consistent with prior NICE recommendations.⁵⁸ In unadjusted analyses, where the EPCORE NHL-1 data are compared with other treatments irrespective of their baseline characteristics, each patient is given a weight of 1 and the data are unchanged. In adjusted analyses, the EPCORE NHL-1 trial data were reweighted to match the baseline characteristics of those reported in the HMRN dataset, using the method of moments as described by Signorovitch et al.⁵⁷

Whenever indicated to improve the accuracy and precision of final parameter estimates, adjustment weights were incrementally truncated at the following thresholds of their distribution to reduce the occurrence of extreme weights (i.e., generally higher than 5-6 or lower than 0.1),⁷⁴ while still preserving the resulting balance in adjusted baseline characteristics, as previously recommended.

2.12.2.1 Endpoints of Interest

Comparative efficacy data for epcoritamab relative to current 4L+ care were derived for:

- PFS (Progression Free Survival) and OS (Overall Survival) Hazard ratio (HR) and 95% confidence interval (CI)
- Kaplan-Meier time-to-event survival curves
- ORR (Overall Response Rate) and CR (Complete Response) Odds ratios (OR) and 95% CI

The EPCORE NHL-1 data and the reconstructed patient-level outcomes data for current 4L+ care were analysed using a weighted Cox model with robust standard errors, using the “survival” package in the statistical software R. The outcome of the survival ITCs were the HRs and 95% CIs of epcoritamab relative to current 4L+ care. A HR<1 indicates lower risk of progression or death for epcoritamab than for the comparator treatment. Weighted Cox regression is a parsimonious option to account for time-dependent effects applicable for small samples sizes. The contributions of each event time to the partial likelihood are weighted according to the product of the survivor function and the inverse cumulative probability of follow-up at that time. Therefore, at

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each event time, their weighting function is proportional to the expected number of participants at risk if censoring had not occurred.

2.12.2.2 Variables for adjustments

Selection of variables for adjustment was taken after careful consideration, balancing the need to align populations between evidence sources, reporting limitations and the desire to preserve effective sample size. In consultation with clinical experts and through preliminary investigation of treatment effect modifiers and prognostic variables measurable in the EPCORE NHL1 clinical trial it was determined that it was important to consider variables within the following categories:

- Age
- Sex
- ECOG performance Status
- Disease Stage
- FLIPI score
- Rapid progression on prior treatments
- Number of prior treatments
- Previous treatment with specific therapies
- Refractory status

These factors are aligned with the variables considered for adjustment in the MAIC analyses conducted vs HMRN in TA627, noting that ECOG and FLIPI are validated prognostic indices (where FLIPI includes age and disease stage). The link between early relapse and survival in FL is described in Casulo et al.,⁷⁵ and previous lines of therapy and time from last treatment are likely to reflect the extent and severity of disease. The factors selected for adjustment were, however, limited by the reporting requirements of the HMRN dataset. In the HMRN dataset, several clinical variables were measured at diagnosis but not measured at the start of 4L+ therapy, meaning it was not possible to appropriately adjust for potential imbalances as the proportions at 4L+ were unavailable. This issue was also discussed as part of TA627 and TA1001,

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where HMRN data had been used and where factors such as FLIPI and ECOG were not available at the time of patients initiating their latest LOT.^{17,68} Indeed, ECOG had not been adjusted for in any prior ITCs from relevant appraisals (i.e. in heavily-pre-treated FL or where the HMRN dataset had been used to inform the comparator arm)^{17,68,19,16}).

While ECOG and FLIPI were not measured at the start of 4L+ therapy in the HMRN dataset and therefore not adjusted for (to avoid biasing in favour of epcoritamab), both are composite measures that may be partially represented by the variables that have been adjusted for. For instance, FLIPI includes components such as age and disease stage, which are both accounted for in the MAIC. Similarly, ECOG is generally reflective of overall fitness and functional status, which may be indirectly captured through some of the included variables, such as age. Therefore, the variables included in the adjustment are expected to account for many of the differences between the patient populations that could affect treatment outcomes, as supported by clinical experts.

The final analysis was conducted using variables of interest following consultation with experts to determine which variables are considered to be confounders, and for which there was a strong degree of evidence for association with survival outcomes (i.e., $p \leq 0.25$).^{76,77} The final list of variables used for the base case analyses was:

- Age (≥ 60)
- Disease stage III - IV (At baseline for EPCORE, at diagnosis for HMRN)
- Sex
- Prior ASCT
- Prior CAR-T
- Prior lines of therapy >4
- POD24 after first line CIT
- Refractory to both anti-CD20 and alkylator therapy
- Refractory to most recent anti lymphoma therapy
- Prior treatment with R²

A summary of the considerations for selecting the variables is presented in Table 27.

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Table 27. Selection of prognostic variables and treatment effect modifiers

Characteristic Level		Recommended by clinical experts?	Prognostic variable or effect modifier in EPCORE NHL-1?		Available at 4L+ for HMRN?	Reason for Inclusion/Exclusion?
			PFS at 36 months?	OS at 36 months?		
Age	< 65	Y	■	■	■	Recommended by clinicians [REDACTED] FLIPI component Adjusted in TA627
	≥ 65					
	≥ 60					
ECOG PS	0	Y	■	■	■	Recommended by clinicians [REDACTED], Data only available at diagnosis in HMRN so unable to accurately adjust for this. Adjusting towards a value from diagnosis would bias in favour of epcoritamab
	1					
	2					
FLIPI	0-1	Y	■	■	■	Recommended by clinicians [REDACTED] Data only available at diagnosis in HMRN so unable to accurately adjust for this. Adjusting towards a value from diagnosis would bias in favour of epcoritamab
	2					
	≥3					
	Unknown					
Stage	1-2	-	■	■	■	Not recommended explicitly by clinicians due to being superseded by the importance of FLIPI [REDACTED] FLIPI component Adjusted in TA627 [REDACTED]
	3-4					
Sex	F	Y	■	■	■	Recommended by clinicians
	M					
	Y					
Prior ASCT	N	Y	■	■	■	Recommended by clinicians [REDACTED]
	Y					
Prior CAR T therapy	N	Y	■	■	■	Recommended by clinicians
	Y					
Prior Lines	2	Y	■	■	■	Recommended by clinicians [REDACTED] Adjusted in TA627 (prior lines of therapy [1 vs. 2 vs. >2])
	3					
	>3					
	≥4					

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Progression within 24 months of first line CIT	N	Y	I	I	I	Recommended by clinicians Adjusted for in TA627
	Y					
Refractory to both anti-CD20 and alkylator therapy	N	Y	I	I	I	Recommended by clinicians [REDACTED]
	Y					
Refractory to most recent anti-lymphoma therapy	N	Y	I	I	I	Recommended by clinicians [REDACTED]
	Y					
Prior R ²	N	Y	I	I	I	Recommended by clinicians [REDACTED] Adjusted for prior rituximab-based treatment in TA627
	Y					

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2.12.3 Results of the MAIC: Epcoritamab vs HMRN

After match-adjusting the EPCORE population to HMRN using all characteristics meeting the criteria for inclusion, approximately 50% of the effective sample size was preserved ($N_{\text{ESS}} = 40$) (Table 28).

Table 28. Baseline characteristics for epcoritamab vs HMRN in 4L+ indication

	Unadjusted Epcoritamab FL (n = 81)	Adjusted Epcoritamab ($N_{\text{eff}} = 40$)	HMRN (n = 81)
Age ≥ 60	69.1%	████	████
Male	65.4%	████	████
Disease Stage III – IV [†]	85.2%	████	████
Prior ASCT	18.5%	████	████
Prior CAR-T	7.4%	██	██
POD24 after first line CIT	37.0%	████	████
Refractory to most recent anti-lymphoma therapy	76.5%	████	████
Refractory to both anti-CD20 and an alkylator	74.1%	████	████
Prior lines of therapy ≥ 4	49.4%	████	████
Prior treatment with R ²	30.9%	████	████

[†] At baseline in EPCORE NHL-1, at diagnosis for HMRN. ASCT, autologous stem cell transplant; CAR T, chimeric antigen receptor (CAR) T-cell therapy; CIT, chemoimmunotherapy; FL, Follicular Lymphoma; N_{eff} , effective sample size.

Figure 16 and Table 29 show the distribution of rescaled weights for patients treated with epcoritamab.

Figure 16. Adjusted EPCORE NHL-1 weights distribution – Epcoritamab vs HMRN in 4L+ indication with summary statistics for weights distribution

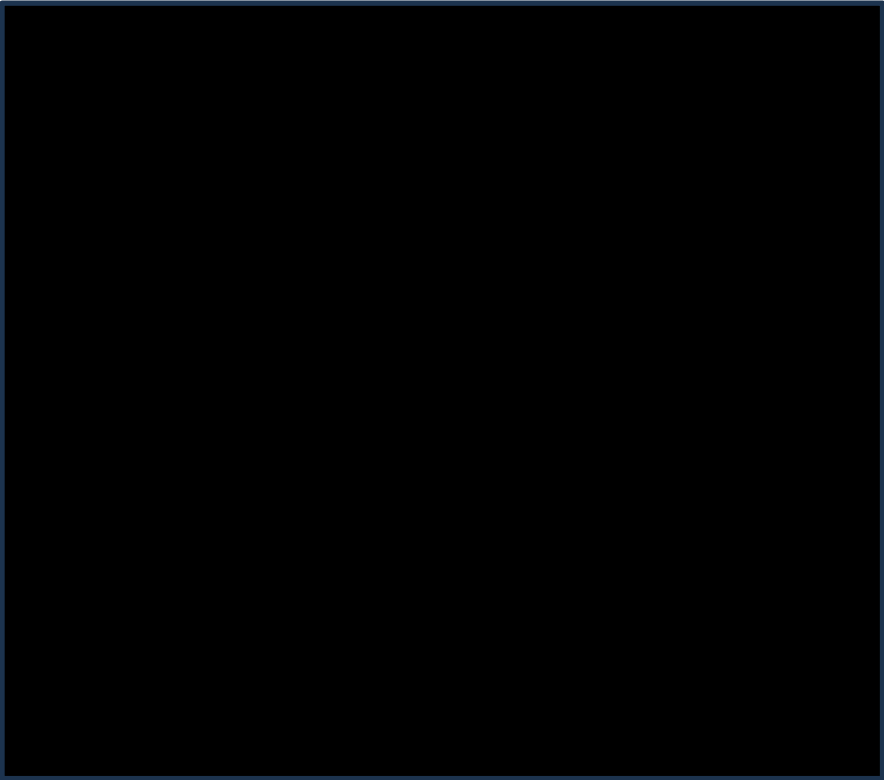


Table 29. Adjusted EPCORE NHL-1 weights distribution – Epcoritamab vs HMRN in 4L+ indication with summary statistics for weights distribution

	Rescaled weight
Min	██████
1 st Quartile	██████
Median	██████
Mean	██████
3 rd Quartile	██████
Max	██████

2.12.3.1 Complete and overall response

Patients treated with epcoritamab in EPCORE NHL-1 showed significantly higher rates of CR or OR compared with patients receiving current 4L+ care in the HMRN dataset (████% vs █████% and █████% vs █████%, for CR and OR, respectively), demonstrating a meaningful improvement in clinical outcomes. Specifically, the adjusted odds ratio for Company evidence submission for epcoritamab for treating relapsed or refractory follicular lymphoma patients after three or more systemic treatments

CR for epcoritamab was [REDACTED] when compared with current 4L+ care, and the adjusted odds ratio for OR was [REDACTED] when compared with current 4L+ care (Table 30).

Table 30. Unadjusted and adjusted best response outcomes for epcoritamab compared with current 4L+ care

	Unadjusted Epcoritamab (N = 81)	Epcoritamab adjusted to HMRN (N _{eff} = 40)
Complete response (CR)	Epcoritamab: [REDACTED] Current 4L+ care: [REDACTED]	Epcoritamab: [REDACTED] Current 4L+ care: [REDACTED]
Odds Ratio [95% CI]	[REDACTED]	[REDACTED]
Overall response (OR)	Epcoritamab: [REDACTED] Current 4L+ care: [REDACTED]	Epcoritamab: [REDACTED] Current 4L+ care: [REDACTED]
Odds Ratio [95% CI]	[REDACTED]	[REDACTED]

CI, confidence interval; CR, complete response; HMRN, Haematological Malignancy Research Network; N_{eff}, effective sample size; OR, overall response

2.12.3.2 OS and PFS

The MAIC-adjusted OS was significantly better for epcoritamab compared with current 4L+ care, with over [REDACTED]% of patients treated with epcoritamab still alive after two years compared with [REDACTED]% of patients still alive at the same time point in the HMRN dataset (adjusted HR = [REDACTED]). Progression-free survival was also significantly better for epcoritamab compared with current 4L+ care, with [REDACTED] of patients ([REDACTED]%) treated with epcoritamab remaining progression free after 2 years (adjusted HR = [REDACTED]) (Table 31). KM curves for the MAIC-unadjusted and -adjusted epcoritamab data and comparator data are presented below for both outcomes (Figure 17).

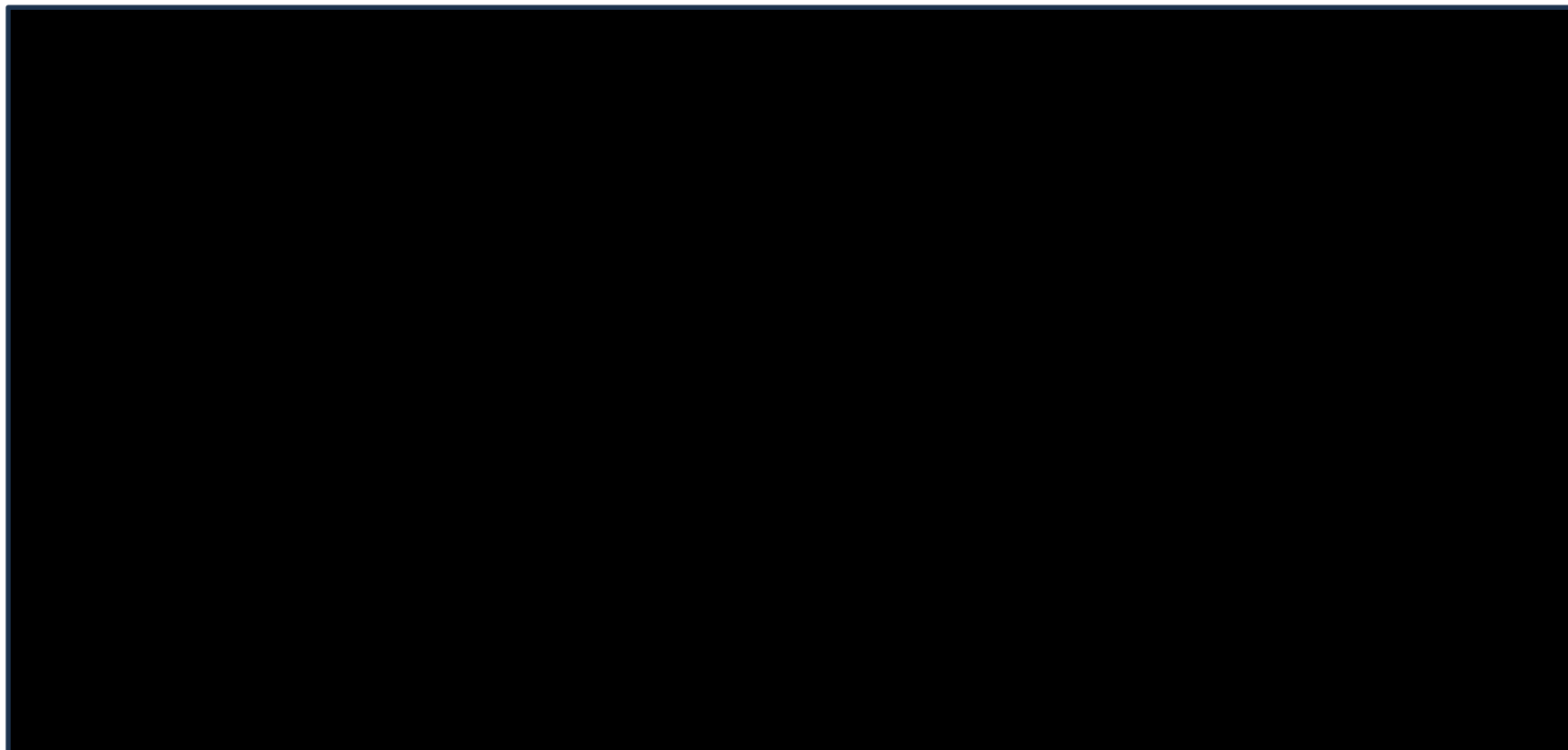
Table 31. Unadjusted and matched MAIC-adjusted OS and PFS for EPCORE NHL-1 vs current 4L+ care in 4L+ indication

OS	HR [95% CI]	p-value
Unadjusted	██████████	████
Adjusted	██████████	████
PFS	HR [95% CI]	p-value
Unadjusted	██████████	████
Adjusted	██████████	████

HR, hazard ratio; MAIC, matching-adjusted indirect comparison; PFS, progression free survival; OS, overall survival

As discussed further in Section 3.3.2, following inspection of the log-cumulative hazards, the Schoenfeld residuals and the Grambsch-Therneau assessment, there is no evidence to suggest that the proportional hazards assumption (PHA) is violated for both PFS and OS.

Figure 17. Unadjusted and adjusted overall survival and progression-free survival for EPCORE- NHL-1 vs HMRN in 4L+ indication



HMRN, Haematological Malignancy Research Network; MAIC, matching-adjusted indirect comparison; OS, overall survival; PFS, progression-free survival

Strengths and weakness of the analyses

Using a relevant dataset, an unanchored MAIC was conducted to estimate the relative efficacy of epcoritamab in 4L+ R/R FL based on the EPCORE NHL-1 trial and an equivalent 4L+ cohort from the HMRN data set. The use of data from HMRN allows us to model a representative sample of UK patients receiving relevant treatments as part of current 4L+ care.

While results from unanchored analyses are sensitive to assumptions of accurately including all available prognostic characteristics and treatment effect modifiers, and the possibility of unaccounted, unobserved residual bias, attempts were made to adjust for all available and clinically relevant baseline prognostic factors and effect modifiers whilst preserving effective sample size. Decisions around variable selection considered clinical expert feedback, tests for significance following investigation of the EPCORE NHL-1 trial, prior NICE appraisals in FL and data reporting limitations in HMRN. Unexplained variation in derived relative treatment effects in the ITC could not be tested for and there may be correlated unobserved disease severity characteristics that remain unadjusted in the comparisons. Nevertheless, extensive effort was made to ensure balance between key characteristics between studies taking into account several relevant sources.

The follow up of the adjusted EPCORE NHL-1 trial data was [REDACTED]. With shorter follow-up time, the number of patients being censored is higher than would be expected in a more mature curve, resulting in a low number of patients at risk towards the end of the current curve. Observed events towards the tail of OS and PFS curves, therefore, have greater influence (i.e., large drops in the curves) than would be expected with more mature data. This effect is further exacerbated when applying patient weights as this more rapidly reduces the effective at-risk denominator used for calculating survival probability. Current results toward the end of the curves may not be fully representative of the effect of treatment on survival.

Although follow-up of patients in HMRN was much longer than in EPCORE NHL-1, the sample size within the HMRN database at 4L+ was relatively small. For the comparison of epcoritamab vs current 4L+ care, the analysis demonstrated a substantial and significant improvement with epcoritamab treatment in OS and PFS. Company evidence submission for epcoritamab for treating relapsed or refractory follicular lymphoma patients after three or more systemic treatments

(adjusted [REDACTED] and adjusted [REDACTED] respectively). Patients treated with epcoritamab in EPCORE NHL-1 were significantly more likely to achieve CR or OR compared with patients treated with current 4L+ care in HMRN. Specifically, the adjusted odds ratio for CR for epcoritamab was [REDACTED] when compared with current 4L+ care, and the adjusted odds ratio for OR was [REDACTED] when compared with current 4L+ care.

2.13 Adverse reactions

2.13.1 Summary of Treatment Emergent Adverse Events

A summary of all treatment emergent adverse events (TEAEs) is presented in Table 32. In the 4L+ FL cohort, the recorded TEAEs were mild and commonly managed by healthcare providers. Grade 3 or higher TEAEs were experienced by [REDACTED] patients. Fatal TEAEs were experienced by [REDACTED]. Adverse events of special interest (AESIs) were experienced by [REDACTED], of which [REDACTED] experienced cytokine release syndrome (CRS) and [REDACTED] experienced immune effector cell-associated neurotoxicity syndrome (ICANS). [REDACTED] experienced clinical tumour lysis syndrome (CTLS) or neutropenic sepsis.

Table 32. Overview of TEAEs, 4L+ FL cohort

	Expansion Part
	4L+ FL (N = 81)
Number of Patients with at least one, N (%)	
TEAE	██████
Related TEAE	██████
Grade 3 and higher TEAE	██████
Grade 3 and higher related TEAE	██████
TEAE by worst toxicity grade, N (%)	
1	██████
2	██████
3	██████
4	██████
5	██████
Serious TEAE	██████
Serious TEAE-related to epcoritamab	██████
TEAE leading to treatment discontinuation	██████
TEAE leading to dose delay	██████
Fatal TEAE	██████
Fatal TEAE-related to epcoritamab	██████
AESI, N (%)	
CRS	██████
ICANS	██████
CTLS	I

Data cut ██████

Note: Percentages calculated on numbers of subjects in SAS. Adverse events classified using MedDRA v26.0 and CTCAE v5.0 and are counted only once per category. ICANS is graded according to Lee et al 2019⁷⁸, CRS as per Lee et al 2019⁷⁸, CTLS according to Cairo-bishop.

AESI, adverse events of special interest; CRS, Cytokine release syndrome; CTLS, clinical tumour lysis syndrome; ICANS, immune effector cell-associated neurotoxicity; TEAE; treatment emergent adverse events

2.13.2 Treatment-Emergent Adverse Events

A summary of the most common TEAEs is presented in Table 33. The most frequently reported TEAEs in the 4L+ cohort were CRS (██████████), COVID-19 (██████████), injection site reactions (37.0%, 30 patients), fatigue (██████████), diarrhoea (██████████), pyrexia (██████████), cough (██████████ patients) and neutropenia (██████████). A total of ██████████ patients had TEAEs considered to be related to epcoritamab with the most common being CRS (██████████) and injection site reaction (██████████). ██████████ (██████████) patients had an infection or infestation TEAE related to epcoritamab.

Table 33. Summary of TEAEs reported in >10% of the population, 4L+ FL cohort

System Organ Class Preferred Term	Expansion Part	
	4L+ FL N = (81)	
	All	Related
Patients with at least one TEAE	██████	██████
Cytokine Release syndrome	██████	██████
Injection site reaction	██████	██████
COVID-19	██████	██████
Fatigue	██████	██████
Diarrhoea	██████	██████
Pyrexia	██████	██████
Neutropenia	██████	██████
Cough	██████	██████
Headache	██████	██████
Anaemia	██████	██████
Injection site erythema	██████	██████
Upper respiratory tract infection	██████	██████
Nausea	██████	██████
Arthralgia	██████	██████
Dyspnoea	██████	██████
COVID-19 pneumonia	██████	██████
Insomnia	██████	I
Oedema peripheral	██████	I
Constipation	██████	██████
Back pain	██████	██████
Neutrophil count decreased	██████	██████
Dizziness	██████	██████
Urinary tract infection	██████	██████
Hypogammaglobulinaemia	██████	██████
Pruritus	██████	██████

Data cut ██████

Percentages calculated based on number of subjects in Safety Analysis Set.

Adverse events are classified using MedDRA v27.0 and are counted only once per system organ class and only once per preferred term.

TEAE, treatment emergent adverse events; ICANs, immune effector cell-associated neurotoxicity

2.13.3 Serious grade 3-4 TEAEs

A summary of serious grade 3-4 TEAEs by system organ class and preferred term (PT) is provided in Table 34. Severe, high-grade treatment related infections were uncommon in the 4L+ cohort (██████████).

Table 34. Summary of serious grade 3 or 4 TEAEs

	Expansion Part	
	4L+ FL (N = 81)	
	All	Related
Subjects with at least one serious TEAE	██████████	██████████
Serious Grade 3-4 TEAEs		
Infections and infestations	██████████	██████████
Blood and lymphatic system disorders	██████████	██████████
Metabolism and nutrition disorders	██████████	██████████
General disorders and administration site conditions	██████████	██████████
Respiratory, thoracic and mediastinal disorders	██████████	██████████

Data cut ██████████

Percentages calculated based on number of subjects in Safety Analysis Set.

Adverse events are classified using MedDRA v26.0 and are counted only once per system organ class and only once per preferred terms.

TEAE, treatment emergent adverse events.

2.13.4 Treatment emergent events leading to discontinuation

In the 4L+ cohort, ██████████ experienced TEAEs that led to trial discontinuation, the most common of which was COVID-19 pneumonia (██████████). TEAEs, by toxicity grade, are presented in Table 35.

Table 35. Summary of TEAEs for 4L+ cohort leading to discontinuation by worst toxicity grade

FL1-3A 4L+ (N = 81)						
Number of subjects, n (%)	Toxicity Grade					
	1	2	3	4	5	Total
Infections and infestations	█	██████	██████	█	██████	██████
COVID-19 pneumonia	█	█	██████	█	██████	██████
COVID-19	█	██████	██████	█	█	██████
Hepatitis E	█	██████	█	█	█	██████
Chronic sinusitis	█	██████	█	█	█	██████
Pseudomonal sepsis	█	█	█	█	██████	██████

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FL1-3A 4L+ (N = 81)						
Number of subjects, n (%)	Toxicity Grade					
	1	2	3	4	5	Total
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	■	■	■■■	■	■■■	■■■
Angioimmunoblastic T-cell lymphoma	■	■	■■■	■	■	■■■
Malignant peritoneal neoplasm	■	■	■■■	■	■	■■■
T-cell lymphoma	■	■	■	■	■■■	■■■
Gastrointestinal disorders	■■■	■	■	■	■	■■■
Diarrhoea	■■■	■	■	■	■	■■■
General disorders and administration site conditions	■	■■■	■	■	■	■■■
Fatigue	■	■■■	■	■	■	■■■
Malaise	■	■■■	■	■	■	■■■
Respiratory, thoracic and mediastinal disorders	■	■	■■■	■	■■■	■■■
Interstitial lung disease	■	■	■	■	■■■	■■■
Pneumonitis	■	■	■■■	■	■	■■■
Cardiac disorders	■	■	■	■	■■■	■■■
Cardiopulmonary failure	■	■	■	■	■■■	■■■

Data cutoff: ■■■■

"-" Not reported

Percentages calculated based on number of subjects in each subgroup.

Adverse events are classified using MedDRA v27.0 and are only counted once per organ class and only once per preferred term at the highest recorded severity. ICANs events are graded according to Lee et al 2019, CRS events as per Lee et al 2019 and CTLS according to Cairo-Bishop. All other events are graded according to CTCAE v5.0.

2.13.5 Adverse events of special interest (AESI)

Bispecific antibodies are now routinely used in the treatment of DLBCL (glofitamab, TA927⁷⁹ and epcoritamab, TA954⁸). CAR-T and bispecific treatments are associated with several common side effects including ICANS and CRS. These side effects are well documented and there is a growing familiarity with recognising and treating these adverse events. These side effects are considered TEAEs and are summarised in Table 36.

ICANS events were reported in ■■■ of patients (■■■) in the 4L+ FL subgroup with 3 of these events (■■■) reported as a Grade 1 event, and the remaining 2 (■■■)

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reported as Grade 2. CRS events were reported in █% of patients (█) in the 4L+ subgroup. █) of these were reported at Grade 1, with the remaining events being reported at Grade 2 (█%) and Grade 3 (█).

Table 36. Summary of AESIs

Number of Patients	Expansion Part
	FL 1-3A 4L+ (N = 81)
Patients with ≥ 1 ICANS event	█
Grade 1	█
Grade 2	█
Grade 3	█
Grade 4	█
Grade 5	█
Patients with ≥1 CRS event	█
Grade 1	█
Grade 2	█
Grade 3	█
Grade 4	█
Grade 5	█

Data cut █

CRS events are graded according to Lee et al 2019

For a subject with multiple events, a subject is defined as resolved if all events are resolved

AESI, adverse event of special interest; CRS, cytokine release syndrome; ICANs, immune effector cell-associated neurotoxicity

2.14 Ongoing studies

This submission presents results from the EPCORE NHL-1 trial (NCT03625037) for the █ cutoff. To provide further context for the safety and efficacy of epcoritamab, data from the C1-Opt cohort (8 January 2024 data cutoff, █ months median follow-up), is provided in this section.

2.14.1 EPCORE NHL-1 – C1-Opt 4L+ Cohort

Following the dose expansion phase of the EPCORE NHL-1 trial, a dose optimisation part was conducted to investigate different step-up doses (SUDs) in order to reduce the risk of ≥ grade 2 CRS observed after the first full dose. The optimisation part was conducted in three cohorts (DLBCL, FL Grades 1-3A and MCL).

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For the FL1-3A cohort, the optimisation part was conducted in two arms; Arm A and Arm B, the dosing regimens for which can be found in Table 37. Initially six participants were enrolled in each arm, with preliminary analysis revealing a numerically lower CRS rate in Arm A compared with Arm B. As such, Arm A was expanded to include 86 participants. The dosing strategy for Arm A is included in the anticipated marketing approval.

Data pertaining to the 4L+ cohort from Arm A is presented in this Section. Data pertaining to the full trial population for FL, representing all patients in Arm A of the Optimisation Part of the trial, can be found in Appendix M.

Table 37. Dose regimen in EPCORE NHL-1 optimisation part

	Priming dose (C1D1)	First Intermediate dose (C1D8)	Second Intermediate dose (C1D15)	First full dose (C1D22)	Second full dose (C2D1)
Arm A	0.16 mg	0.8 mg	3 mg	48 mg	48 mg
Arm B	0.16 mg	0.8 mg	6 mg	48 mg	48 mg

An overview of the outcomes reported as part of the EPCORE NHL-1 Optimisation Part and associated statistical strategy are summarised in Table 38.

Table 38. Statistical analysis and outcomes reported for the EPCORE NHL-1 Optimisation Part

	C1- Dose Optimisation
Reported outcomes specified in the decision problem	PFS OS
Other outcomes reported	Pharmacodynamic markers in blood samples
Hypothesis objective	No formal hypothesis testing was performed on the FL optimisation cohort. Analysis of the trial patients and efficacy were performed on the FAS, defined as all subjects that had been exposed to epcoritamab. Safety analysis was performed on the SAS. Sensitivity analysis was performed using the additional predefined analysis population.
Statistical Analysis	See Section 2.6.2
Sample size power calculation	For the FL optimisation cohort, a sample size of 80 patients at the selected dose regimen would provide more than 80% power to detect an event with a true event rate at 2% or higher.

FL, follicular lymphoma; OS, overall survival; PFS, progression free survival; SAS, safety analysis set

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2.14.2 Clinical evidence – C1-Opt 4L+ Cohort

An overview of the patient baseline demographics and disease characteristics is presented in Table 39. The gender of participants in the C1-Opt 4L+ cohort was well matched (n = 20, 48.8% and n = 21, 51.2% male and female, respectively). Race was not reported in 22.0% of patients (9 patients) with 75.6% of patients (n = 31) being reported as white. Mild or moderate renal impairment was reported in 61.0% (n = 25) patients, with severe renal impairment not being reported in any patient. The majority of patients (95.1%, 39 patients) had normal hepatic function.

Approximately half of the cohort (53.7%, 22 patients) had FL at histological Grade 2, with Grade 1 and Grade 3A being represented at 26.8% (11 patients) and 14.6% (6 patients), respectively. A FLIPI score of 3 or greater was reported in 63.4% of the cohort (26 patients). Double refractory disease was reported in 65.9% of patients (27 patients).

Table 39. FL1-3A Patient Baseline Demographic and Disease Characteristics, C1-Opt 4L+ cohort

	Optimisation Part, Arm A
	C1-Opt 4L+ (N = 41)
Age at informed consent (years)	
Mean (SD)	65.5 (8.99)
Median	66.0
Min, Max	46, 81
Sex (at birth)	
Male	20 (48.8%)
Female	21 (51.2%)
Race	
White	31 (75.6%)
Black or African American	0
Asian Other	1 (2.4%)
Not reported	9 (22.0%)
Ethnicity	
Hispanic or Latino	2 (4.9%)
Not Hispanic or Latino	9 (22.0%)
Not reported	0

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BMI (kg/m ²) category at baseline	
<18.5	0
18.5 ≤ 25.0	18 (43.9%)
25 ≤ 30	16 (39.0%)
≥ 30.0	5 (12.2%)
Missing	2 (4.9%)
ECOG Performance status	
0	25 (61.0%)
1	16 (39.0%)
2	0
Baseline renal function classification by Cockcroft- Gault method (CrCl)[mL/min]	
Normal (≥ 90)	16 (39.0%)
Mildly impaired (60 – <90)	17 (41.5%)
Moderately impaired (30 – <60)	8 (19.5%)
Severely impaired (15 – <30)	0
Baseline hepatic function per NCI criteria ⁵⁹	
Normal	39 (95.1%)
Mild Dysfunction	2 (4.9%)
Moderate dysfunction	0
Severe dysfunction	0
Histological grade	
1	11 (26.8%)
2	22 (53.7%)
3A	6 (14.6%)
Unknown	2 (4.9%)
Time from diagnosis to first treatment ^a	
Mean (SD)	10.3 (5.82)
Min, Max	0.9, 33.1
FLIPI	
0-1	5 (12.2%)
2	10 (24.4%)
≥3	26 (63.4%)
Unknown	0
POD24	
POD24 from any first line treatment	19 (46.3%)
POD24 from first time use of immunochemotherapy regardless of line	18 (43.9%)
Double-refractory Status	

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Double refractory to anti-CD20 and alkylating agents, regardless of two treatments being in the same or different treatment lines	27 (65.9%)
Bone Marrow Involvement	
Bone marrow involvement at baseline by investigator	10 (24.4%)

Data cut 8 January 2024, assessed by investigator Arm A: Priming 0.16mg, Intermediate 0.8mg, Second intermediate 0.16mg
a. Time from diagnosis of disease recorded at time of study entry
BMI, body mass index; ECOG, Eastern cooperative oncology group; FL, follicular lymphoma; FLIPI, follicular lymphoma international prognostic index; NCI, National Cancer Institute; SLL, small lymphocytic lymphoma; POD24, progression of disease 24 months.

2.14.3 Overview of clinical effectiveness – C1-Opt 4L+ cohort

A summary of the clinical effectiveness in the C1-Opt 4L+ cohort is summarised in Table 40. Less than ████████ of patients (████%, █████ patients) experienced a progression event and ████████ (████%) died between the initiation of the optimisation part and the 8 January 2024 data cut.

Table 40. Overview of clinical effectiveness, C1-Opt 4L+ cohort

	Optimisation part, Arm A
	C1-Opt 4L+ (n = 41)
OS (months)	
Number of events	██████
Number censored	██████
Min, Max	██████
Median (95% CI) ^a	██████
PFS (months)	
Number of events	██████
Number of censored	██████
Min, Max	██████
Median (95% CI) ^a	██████

Data cut 8 January 2024, assessed by investigator. Arm A: Priming 0.16mg, Intermediate 0.8mg, Second intermediate 0.16mg
a. Based on Kaplan-Meier estimates.
Symbol '+' indicates a censored value
CI, confidence interval; NR, not reported; OS, overall survival; PFS, progression free survival

2.14.4 Clinical effectiveness – C1-Opt 4L+ Cohort

2.14.4.1 Progression-free survival – C1-Opt 4L+ Cohort

Progression or a mortality event was observed in [REDACTED] ([REDACTED]%; [REDACTED] patients) of patients, with a median follow up time of [REDACTED] months. Of the evaluable patients at 6 months, [REDACTED]% remained progression-free (Table 41). These outcomes follow the pattern seen in the 4L+ cohort of the dose expansion study, whereby many events occurred within the first 3 to 6 months and were subsequently followed by a flattening of the KM curve afterwards (Section 2.8.3.3).

Table 41. Progression Free Survival, C1-Opt 4L+ FL Cohort

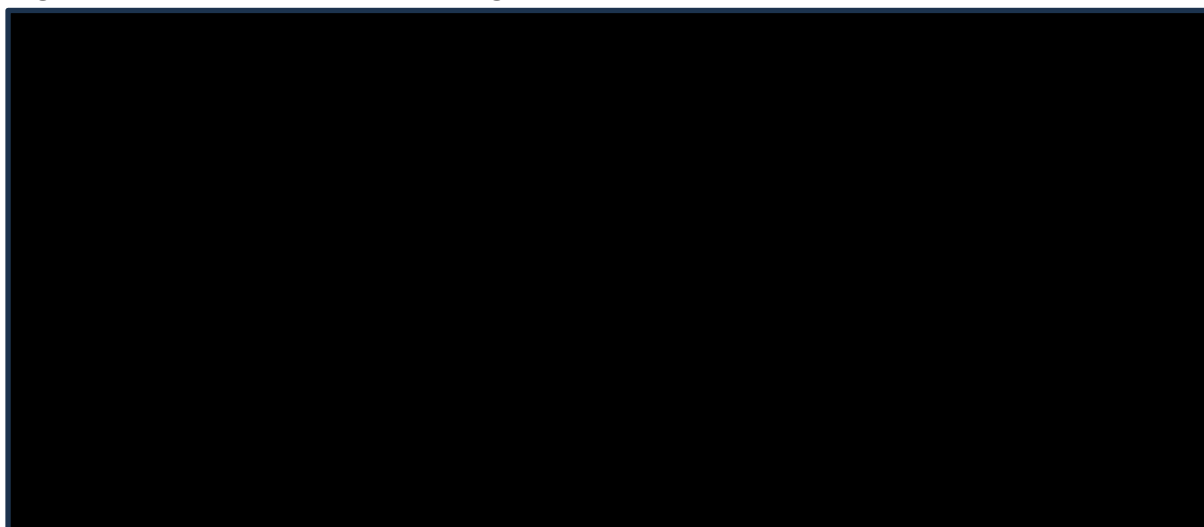
	Optimisation Part, Arm A
	C1-Opt 4L+ (N= 41)
Number of Events	[REDACTED]
Number of Censored	[REDACTED]
Reason for censoring	
Clinical Cutoff	[REDACTED]
No post-baseline assessments	[REDACTED]
PFS (months)	
Median follow-up (95%CI) ^a	[REDACTED]
Median (95% CI) ^b	[REDACTED]
Estimated percentage of patients remaining progression-free (95% CI)^b	
6-month	[REDACTED]
12-month	I
18-month	I

Data cut 8 January 2024, assessed by investigator. Arm A: Priming 0.16mg, Intermediate 0.8mg, Second intermediate 3mg

a. Based on reverse Kaplan-Meier estimate. b. Based on Kaplan-Meier estimate

CI, confidence interval, NR, not reached

Figure 18:Kaplan-Meier Plot of progression-free survival, C1-Opt 4L+ FL Cohort



Data cut 8 January 2024, assessed by investigator. Arm A: Priming 0.16mg, Intermediate 0.8mg, Second intermediate 3mg
CI, confidence interval; FL, follicular lymphoma; NR, not reached

2.14.4.2 Overall survival, C1-Opt 4L+ Cohort

Overall survival in the C1-Opt 4L+ cohort is presented in Table 42 and Figure 19. Deaths were observed in █% (█) of patients in the C1-Opt 4L+ cohort, with a median follow-up time of █ (████) months. At 6-months, █% of patients remained alive. As discussed in Section 2.6.2.1, the dose optimisation part of EPCORE NHL-1 took place outside of the Omicron wave of the COVID-19 pandemic. As of the 8 January 2024 data cut off, █ COVID-19 associated deaths were recorded for the C1-Opt 4L+ cohort, providing a positive indicator of how epcoritamab is expected to perform in a current clinical setting.

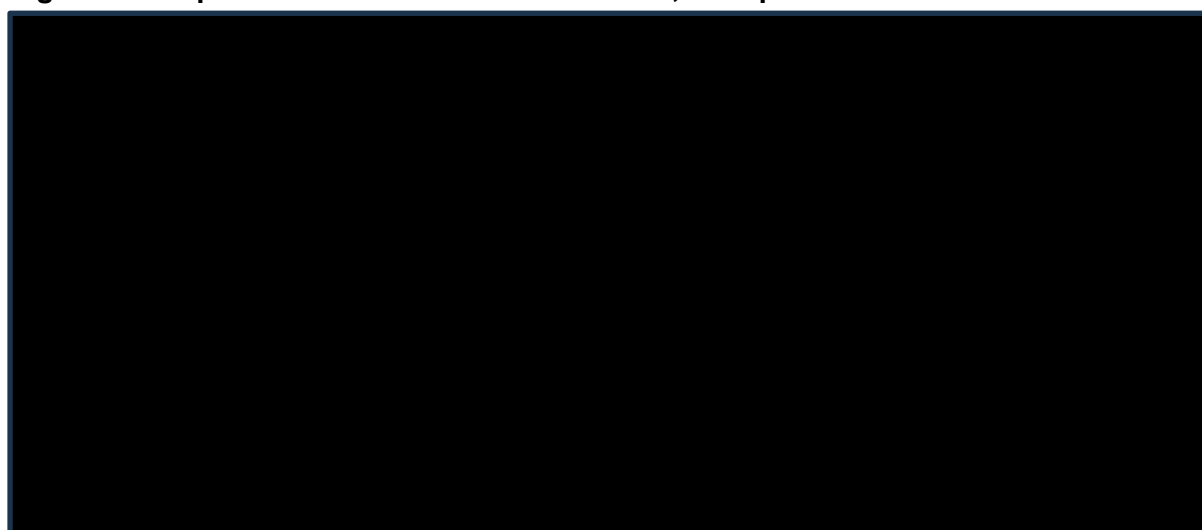
Table 42. Overall Survival, C1-Opt 4L+ Cohort

	Optimisation Part, Arm A
	C1-Opt 4L+ (N= 41)
Number of events	██████
Number of Censored	██████
OS (months)	
Median follow-up (95%CI) ^a	██████████
Median (95% CI) ^b	██████
Estimated percentage of patients remaining alive (95% CI)^b	
6-month	██████████████████
12-month	█
18-month	█

Data cut 8 January 2024, assessed by investigator. Arm A: Priming 0.16mg, Intermediate 0.8mg, Second intermediate 3mg

a. Based on reverse Kaplan-Meier estimate. b. Based on Kaplan-Meier estimate

CI, confidence interval; NR, not reached; OS, overall survival

Figure 19: Kaplan-Meier Plot of Overall Survival, C1-Opt 4L+ FL cohort

Data cut 8 January 2024, assessed by investigator. Arm A: Priming 0.16mg, Intermediate 0.8mg, Second intermediate 3mg
CI, confidence interval; FL, follicular lymphoma; NR, not reached

2.15 Interpretation of clinical effectiveness and safety evidence

2.15.1 Principal findings from the clinical evidence base

Although often considered indolent at an early stage, late-stage FL is an aggressive disease with patient prognosis being poor. Median survival for patients at 4L+ is █████ months, with patients often experiencing disease progression or death within a median of █████ months.⁵ Once a patient reaches 4L+ treatment, they have usually

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exhausted the available treatment options and are often rechallenged with agents from prior treatment lines despite diminishing response rates being observed.⁴ Consequently, there is a significant need for new treatments for this patient population, a challenge exacerbated by the absence of recent innovations meeting the standards needed for NICE approval.

Current treatment options for patients with FL are often delivered via intravenous infusion, which confer a significant burden on patients, carers, and the healthcare system due to their invasive administration. As such there is need for a novel therapy, administered in a convenient fashion that offers clinically and statistically meaningful OS and PFS responses.

Findings from EPCORE NHL-1

Clinical effectiveness

The clinical efficacy evidence base for epcoritamab as a treatment in adult patients with 4L+ R/R FL is informed by the EPCORE NHL-1 trial. In the trial, a total of 81 patients with 4L+ FL were treated with epcoritamab. In this population, the median follow-up for OS was [REDACTED] months, at which point [REDACTED] ([REDACTED] DCO), while the median follow-up for PFS was [REDACTED] months, with median PFS of [REDACTED] months. During the EPCORE NHL-1 trial, [REDACTED]% of patients treated with epcoritamab were still alive after 18 months, and [REDACTED]% were alive after 36 months, demonstrating the durable survival benefits that epcoritamab provides to this late-stage patient population with high unmet clinical need.

Further, epcoritamab treatment resulted in meaningful responses in patients, where OR was reported in [REDACTED] of patients, CR achieved in [REDACTED] of patients, and PR achieved in [REDACTED] of patients. The median DOR follow-up time was [REDACTED] months, with [REDACTED]% and [REDACTED]% of patients remaining in response at 12 and 18 months, respectively. After a median follow up time of [REDACTED] months, the median DOCR was [REDACTED], with [REDACTED]% and [REDACTED]% of patients estimated to remain in CR at 18 and 36 months, respectively.

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To further support the efficacy of epcoritamab, data from the Optimisation Part of the EPCORE NHL-1 trial has been presented (Section 2.14), in which, following a relatively short follow-up, █% of patients remained alive (median follow-up of █ months).

Findings from the MAIC

EPCORE NHL-1 is a single armed trial. As such an ITC, in the form of an unanchored MAIC, was conducted to provide comparative efficacy evidence versus the current treatment options available for patients with 4L+ R/R FL.

For the comparison of epcoritamab vs current 4L+ care for adjusted outcomes, patients treated with epcoritamab in EPCORE NHL-1 were significantly more likely to experience CR or OR compared with patients receiving current 4L+ care as per the HMRN dataset. Specifically, the adjusted odds ratio for CR for epcoritamab was █ when compared with current 4L+ care, and the adjusted odds ratio for OR was █ when compared with current 4L+ care. Further, the analysis demonstrated a significant improvement with epcoritamab treatment in OS and PFS (adjusted █ and adjusted █, respectively).

Safety data on epcoritamab

Bispecific therapies are already available in UK clinical practice to treat DLBCL (epcoritamab, TA954⁸⁰ and glofitamab, TA927).⁷⁹ As such, health care professionals are becoming increasingly familiar with recognising and managing their associated TEAEs. In the 4L+ cohort of the EPCORE NHL-1 trial, Grade 3 or higher TEAEs were experienced by █% of patients (█), with fatal TEAEs being experienced by █% of patients (█), of which █ was considered treatment-related. When considering AESIs, █ of trial participants experienced CRS and █ experienced ICANs. █ cases of CTLs were reported during the trial. Of these AESIs, █ Grade 3, with the remaining AESIs being Grade 2 or below. Therefore, epcoritamab was demonstrated to provide tolerable treatment for this patient population who have been exposed to multiple prior therapies, with a safety profile in line other indications for epcoritamab.^{79,80}

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In order to reduce the number of AEs on treatment with epcoritamab, an alternate dosing strategy was adopted for the C1-Optimisation cohort, including a second intermediate dose of 3 mg, not included in the treatment of the initial FL1-3A or 4L+ cohorts. This dose represents the dosing regimen that will be used in clinical practice. Safety outcomes for the 4L+ C1-Opt cohort are unavailable at the time of submission; however, a comparison of safety outcomes between the dose expansion cohort and C1-Opt cohort for the 3L+ population are presented in Appendix M and demonstrate reduced prevalence and severity of AEs in the dose optimisation cohort.

2.15.2 Strengths and limitations of the clinical evidence base

Strengths

The EPCORE NHL-1 trial provides evidence on the efficacy and safety of epcoritamab for the treatment for adults with 4L+ R/R FL.

[REDACTED], though this submission focuses on the pre-specified 4L+ subpopulation which is considered to have the most urgent unmet need. A high proportion of patients enrolled in the EPCORE NHL-1 trial were from European countries, with [REDACTED] patients ([REDACTED]%) of patients originating from the UK.⁷ Clinical experts were in consensus that the study was generalisable to clinical practice in the UK, with the fitness of the trial population either closely reflecting the fitness of patients in clinical practice or presenting with higher-risk features than seen in real world populations.⁹

A range of endpoints, including those outlined in the NICE scope, which are clinically relevant to this late-stage patient population were evaluated in EPCORE NHL-1. Where relevant, outcomes were assessed by both IRC and investigator assessments. IRC results are generally considered more robust, as Investigators may have individual biases in their assessment.⁸¹ The IRC results were consistent with investigator assessed results. As of the [REDACTED] data cut, OS had not fully matured (median follow-up time [REDACTED] months), demonstrating the efficacy of epcoritamab in the 4L+ FL population, a patient population with poor prognostic outcomes (an OS of [REDACTED] months with current treatment options).⁵ No new safety concerns were identified following epcoritamab treatment. Company evidence submission for epcoritamab for treating relapsed or refractory follicular lymphoma patients after three or more systemic treatments

The clinical evidence presented as part of this submission has been derived from a recent SLR that was conducted according to the principles of systematic reviewing published in the Cochrane handbook.⁸² The clinical SLR identified the pivotal clinical trial EPCORE NHL-1 as the primary evidence source for epcoritamab in patients with R/R FL. The results of the EPCORE NHL-1 trial are relevant to the decision problem outlined in the NICE scope, specifically the population of interest; adult FL patients with R/R 4L+ FL.

Due to an absence of direct trial evidence comparing epcoritamab with current 4L+ care, an unanchored MAIC was used to generate comparative efficacy evidence. After careful consideration, the HMRN registry (which has previously been used in TA604, TA627 and TA1001) was used as a comparator as it is a UK-specific dataset, which was most comparable to the submission population as determined by UK clinical experts.^{9,17,68,83} The evidence used to inform the MAIC considered the best data available on the comparator therapies available in UK clinical practice, accurately reflecting the patient population under consideration according to feedback from UK clinicians.⁹ The MAIC was conducted following the robust methodologies outlined in the NICE guidance in TSD18.⁵⁸ In particular, the effect modifiers and prognostic variables were carefully considered, and were selected based on feedback from UK clinical experts, published literature and testing of prognostic status. This resulted in a high-quality analysis, providing the best estimates for comparative efficacy that could be conducted using the data available. In the MAIC, epcoritamab demonstrated significant and sustained benefits over the comparator arm with OS and PFS hazard ratios of [REDACTED] and [REDACTED]), respectively.

The EPCORE NHL-1 trial was powered to demonstrate statistical significance. Comparative evidence was generated using a UK dataset (HMRN), as per previous TAs, and the NICE recommended approach to reduce the risk of confounding. Therefore, analyses using EPCORE NHL-1 and HMRN detected a statistically significant improvement in OS and PFS of a magnitude that is clinically important to patients with 4L+ R/R FL. Given the high unmet need for additional effective treatment options for patients with 4L+ R/R FL, AbbVie considers that the NHS and patients

would benefit from epcoritamab being prioritised for evaluation based on the data available from the phase Ib/II trial EPCORE NHL-1.

2.15.3 Conclusions

There are limited treatment options for patients starting their fourth LOT. By this stage, their FL is an end-of-life disease characterised by frequent hospitalisations and poor HRQoL.⁵ Epcoritamab introduces a novel mechanism of action to the current treatment strategy for patients with relapsed or refractory FL grades 1-3A at 4L+, providing a completely new treatment option instead of reusing ineffective available therapies. The convenient method by which epcoritamab is delivered has the potential to reduce the utilisation of hospital resources, decrease appointment times and reduce the overall burden experienced by the patient, their care givers and healthcare system.

3 Cost effectiveness

A cost-utility analysis was performed using a partitioned survival model (PSM) structure in line with previous NICE TAs evaluating the cost-effectiveness of interventions for FL

- The objective of this analysis was to evaluate the cost-effectiveness of epcoritamab in patients with 4L+ R/R FL. The analysis compares epcoritamab with a basket of current 4L+ treatment options identified by the HMRN dataset, validated by UK clinicians and aligned with the treatments described in the scope of this appraisal.
- A PSM was developed using three health states:
 - Progression-free: includes patients who are alive and whose disease has not progressed.
 - Progressed disease: includes patients who are alive but whose disease has progressed.
 - Death: includes patients who have died either from disease or other causes.

Survival analyses

- The proportional hazards assumption was assessed on OS and PFS outcomes from EPCORE NHL-1 and the HMRN dataset using the guidance described in NICE DSU TSD 14.⁷²
- Results of the log-cumulative hazards plot, Schoenfeld residuals and Grambsch-Thurneau assessments found no evidence that the assumption of proportional hazards between EPCORE NHL-1 and HMRN is violated; therefore, PFS and OS for current 4L+ care is generated within the model using HRs obtained from the MAIC and compared with the EPCORE NHL-1 survival curves, outlined in Section 2.12.
- Base case parametric distributions were selected using guidance from NICE DSU TSD 14, and were based on visual fit, clinical plausibility and fit statistics.⁷²
- TTD data for HMRN were modelled using extrapolated KM data from HMRN due to the difference in regimen treatment schedules which reduces the ability to assume proportional hazards.

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Utility analyses

- EPCORE NHL-1 included assessment of health-related quality of life during the study, which was used to derive health state utility values. A standardised measure of health status, the EQ-5D-3L, was used, aligned with NICE methods guidance.⁸⁴
- As detailed in Section 2, significantly more patients achieve CR on treatment with epcoritamab compared with treatment with current 4L+ care. In line with comments from healthcare professionals that patients achieving CR are expected to have improved HRQoL compared with patients who do not achieve CR, a weighted utility was applied in the base case to the progression-free health state depending on the proportion of patients achieving CR with epcoritamab and current 4L+ care.
- A utility value of [REDACTED] was applied for patients in the PF health state receiving epcoritamab, while a utility value of [REDACTED] was applied in the PF health state for patients receiving current 4L+ care, reflecting the substantial differences in CR rates observed.
- To measure HRQoL in the PD health state, a utility decrement from Wild et al. was applied to the current 4L+ care PF value to generate a treatment independent health state utility for PD ([REDACTED]), as has been accepted in prior appraisals.⁸⁵

Cost-effectiveness results

- All cost-effectiveness results presented within this submission use the current epcoritamab PAS price.
- The comparator arm, current 4L+ care, is associated with 0.9851 QALYs; therefore, considering a patient population with mean age 64.8 years and 34.6% female, the threshold for applying the ×1.2 severity modifier has been met and is considered in this analysis.
- The total costs associated with epcoritamab and current 4L+ care are £[REDACTED] and £[REDACTED], respectively. The total QALYs associated with epcoritamab and current 4L+ care are 5.176 and 1.182, respectively (×1.2 modifier applied).

- When applying the severity modifier, the resulting ICER for epcoritamab compared with current 4L+ care is £[REDACTED]/QALY, demonstrating that epcoritamab is a cost-effective use of NHS resources when compared with current 4L+ care in patients with 4L+ R/R FL. When no severity modifier is applied, the resulting ICER is £[REDACTED]/QALY.

Sensitivity analyses

- Sensitivity and scenario analyses demonstrate that the model results are robust to parameter and input uncertainty and consistently show epcoritamab to be associated with ICERs within the range NICE would usually consider to be cost-effective.

Conclusions

- The results of the economic analyses presented in this submission demonstrate that epcoritamab represents a cost-effective use of NHS resources compared with current 4L+ care in patients with R/R FL.

3.1 Published cost-effectiveness studies

In line with the NICE technology evaluations manual, an SLR was conducted to identify all relevant cost-effectiveness studies in FL. The SLR was conducted in alignment with the CRD's guidance for systematic reviews,⁸⁶ the Cochrane Handbook for Systematic Reviews,⁸⁷ Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines,⁸⁸ and requirements set out by NICE.⁸⁹ Details of the SLR are provided in Appendix E.

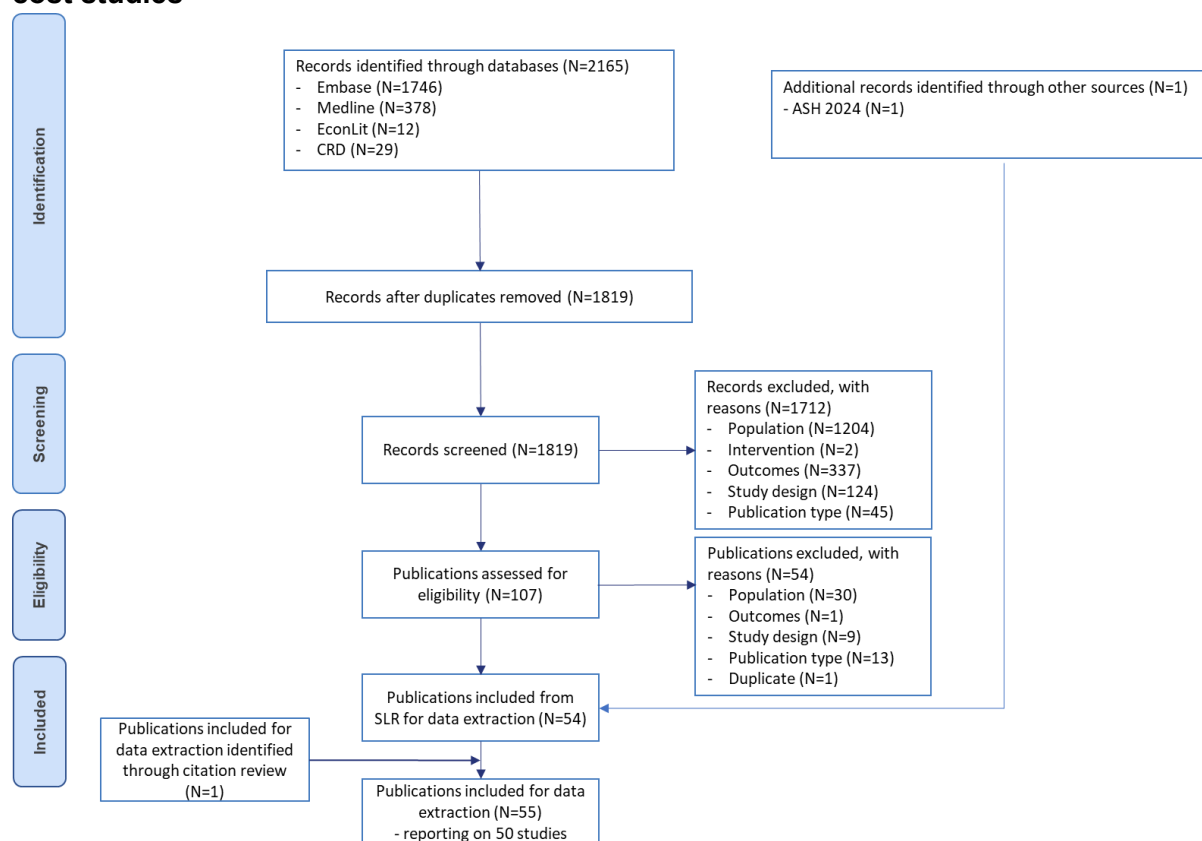
In brief, electronic databases (Embase, Medline and EconLit) were searched from inception to 03 April 2023, and subsequently updated on 07 November 2024. Conference proceedings between 2020 and 2024 were indexed in Embase and were therefore captured in the electronic database search. Additional searches were performed on the websites of HTA authorities to retrieve critical appraisals and key learnings from previous assessments. To identify relevant articles, search terms for FL were used in the website's search engines. HTA authorities considered for inclusion in the SLR were NICE, Canadian Agency for Drugs and Technologies in Health (CADTH), Scottish Medicines Consortium (SMC), Gemeinsamer Company evidence submission for epcoritamab for treating relapsed or refractory follicular lymphoma patients after three or more systemic treatments

Bundesausschuss/Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (G-BA/IQWiG), Haute Autorité de Santé (HAS), Pharmaceutical Benefits Advisory Committee (PBAC), National Institute for Health Research (NIHR) HTA library, and the International Network of Agencies for Health Technology Assessment (INAHTA) database.

A PRISMA diagram for the economic search, which included a search of resource use and cost studies, is presented in Figure 20.

The outcomes of the economic search are presented in Appendix F.

Figure 20. PRISMA flow diagram for SLR of economic evaluations, resource use and cost studies



ASH, American Society of Hematology; CRD Centre for Reviews and Dissemination; EMBASE, Excerpta Medica database; Medline; medical literature analysis and Retrieval System; SLR, systematic literature review.

Among the 55 publications identified in the SLR for economic evaluations and cost and resource use, 37 of them (reporting on 35 studies) presented economic evaluations. The evaluations predominantly utilised Markov models (n=13), followed by partitioned survival models (n=11), budget impact models (n=7), and cost-minimisation models (n=4). Most evidence originated from Europe and North Company evidence submission for epcoritamab for treating relapsed or refractory follicular lymphoma patients after three or more systemic treatments

America, with limited representation from other regions. The majority of the economic models adopted a payer perspective, with limited consideration for societal impacts, indicating a research gap regarding broader healthcare impacts such as productivity loss for patients with FL.

A summary of published cost-effectiveness studies identified within the company's economic SLR is presented in Appendix E.

3.2 Economic analysis

The economic case presented in this submission is based on a conventional cost-utility analysis, assessing the use of epcoritamab for the treatment of adults with 4L+ R/R FL. The analysis considers the simple discount patient access scheme (PAS) available for epcoritamab.

3.2.1 Patient population

The model considered the R/R FL patient population that has received three or more prior lines of systemic therapy.

Baseline mean age and gender distribution were used to estimate age- and gender-specific mortality of the general population. Mean weight and body surface area (BSA) was used to calculate weight- or BSA-dependent dose of drugs (for subcutaneous and intravenous drugs).

Table 43. Population baseline characteristics

Parameter	Value	Source
Mean age (SE), years	64.80 (1.23)	EPCORE NHL-1, using the FL cohort receiving three or more prior systemic treatments ⁹⁰
Female proportion (SE), %	34.60% (0.053%)	
Mean bodyweight (SE), kg	77.40 (1.78)	
Mean BSA (SE), m ²	1.90 (0.02)	

BSA, body surface area; FL, follicular lymphoma; SE, standard error
BSA is calculated by the Dubois formula: $BSA = 0.007184 \times \text{Height(m)}^{0.725} \times \text{Weight(kg)}^{0.425}$

3.2.2 Model structure

In line with previous R/R FL appraisals, a partitioned survival model (PSM) structure was adopted to estimate the cost-effectiveness of epcoritamab versus current 4L+ care.⁹¹⁻⁹⁴ The cost-effectiveness model was developed in line with NICE guidelines related to the methods of technology appraisals.⁸⁴

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The model adopts three health states;

- Progression-free (PF): includes patients who are alive and whose disease has not progressed.
- Progressed disease (PD): includes patients who are alive but whose disease has progressed.
- Death: includes patients who have died either from disease or other causes

This three-state PSM structure was selected because it offers a data-driven, flexible approach that is well-established in economic modelling of oncological diseases, particularly in R/R FL (Table 44). PSMs have the advantage of directly incorporating observed survival data (such as PFS and OS), which reduces the uncertainty that can arise when estimating separate transition probabilities required in a state-transition (Markov) model. This approach minimises reliance on additional assumptions about intermediate health state transitions—a significant benefit when intermediate endpoint data are limited or potentially biased. Given the single arm nature of the ECPORE NHL-1 trial, patient-level data was not available for current standard of care 4L+ outcomes; the PSM allows for survival-based comparisons using aggregate-level data from HMRN. Additionally, the use of a PSM is consistent with the approach taken in TA604, TA627 and TA1001, where modelling comparative efficacy utilised data from HMRN.^{17,68,83}

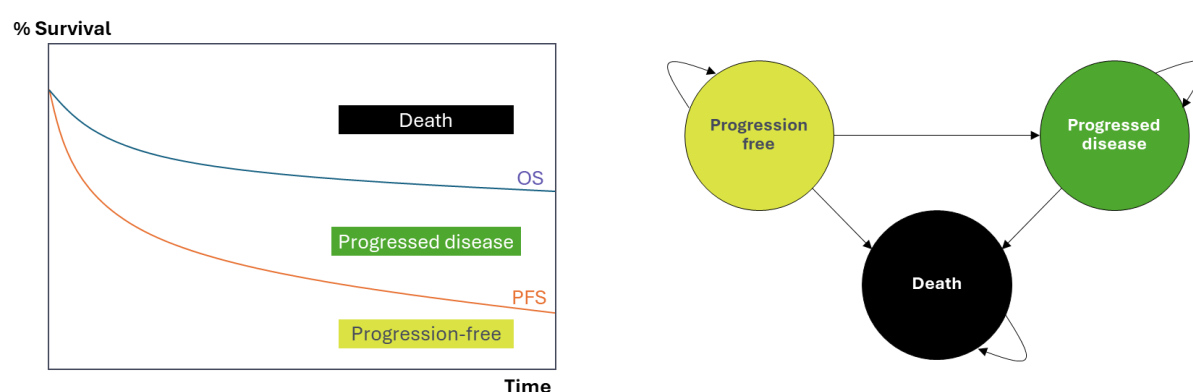
The proportion of patients within each health state was determined by OS and PFS curves via an area-under-the-curve approach using data from the EPCORE NHL-1 trial and the comparator data source, HMRN, with outcomes being individually modelled following adjustments performed via a MAIC (Figure 21). The methods and outcomes of the MAIC are described in Section 2.12

All patients enter the model in the PFS health state and remain in this state until disease progression or death. If a patient's disease progresses, they move into the progressed disease health state where they remain until their death. Death is an absorbing health state.

The PFS curve determines the proportion of patients remaining alive and progression-free, and the OS curve determines the proportion of patients that are alive (regardless of their progression status). The difference between the PFS and OS curves informs the proportion of patients that are alive post-progression.

Background mortality is incorporated in survival extrapolations (described in Section 3.3.2.3) to ensure that the OS of patients within the model does not exceed the survival of an age- and sex-matched population within the UK.

Figure 21. Survival curves informing the proportion of patients per health state



OS, overall survival; PFS, progression-free survival

Patients accrue costs and utilities for each cycle they spend in each state (excluding death) and the model is run over a defined number of cycles, allowing an estimate of total costs and quality-adjusted life years (QALYs) for the cohort over the specified time horizon. The direct healthcare costs include treatment acquisition costs, administration costs, healthcare resource costs per health state, costs of subsequent treatment following treatment discontinuation, AE management costs, costs of disease progression, and costs of terminal care.

3.2.2.1 Time horizon

The model considers a lifetime time horizon in the base case analysis. The NICE guidelines recommend that the time horizon is sufficiently long to reflect any differences in costs or outcomes between the technologies that are being compared.⁹⁵ With a mean age at the start of the model of 64.80 as informed by the cohort receiving 4L+ treatment in the EPCORE NHL-1 trial at enrolment, this leads to

a lifetime horizon spanning 35.2 years. The impact of a shorter time horizon is explored in scenario analyses (Section 3.11.3).

3.2.2.2 Cycle length

The model adopts a cycle length of one week. This is considered sufficiently short to accurately capture model outcomes, hence no half-cycle correction is applied.

3.2.2.3 Perspective and discounting

The model considers a NHS and PSS perspective, and costs and health-related utilities are discounted at 3.5% per annum in accordance with the NICE reference case.⁸⁴

Table 44 summarises the key features of the economic analysis in comparison with previous appraisals in the same disease area within the R/R setting.

Table 44. Features of the economic analysis

Factor	Previous appraisals						Current appraisal	
	TA894 (Axicabtagene ciloleucel)	TA892 (Mosunetuzumab)	TA629 [†] (Obinutuzumab + Bendamustine)	TA627 (R ²)	TA604 (Idelalisib)	TA137 (Rituximab)	Chosen approach	Description
Model structure	Partitioned survival analysis	Partitioned survival analysis	Partitioned survival analysis	Partitioned survival analysis	Cohort-level state transition model and partitioned survival analysis for the HMRN comparison	Partitioned survival analysis	Partitioned survival analysis	Captures the clinical benefits of epcoritamab and is aligned with previous NICE appraisals of treatments for follicular lymphoma.
Time horizon	Lifetime (40 years)	Lifetime (40 years)	Lifetime (25 years)	Lifetime (40 years)	Lifetime (38 years)	Lifetime (30 years)	Lifetime (35.2 years)	Consistent with NICE reference case.
Cycle length	28 days (half-cycle correction applied to costs and outcomes)	One week (half-cycle correction applied)	NR	28 days (half-cycle correction applied)	One week (no half-cycle correction applied)	Monthly (half-cycle correction applied)	One week (no half-cycle correction applied)	Sufficiently short to accurately capture model outcomes.
Discount rate	Costs and QALYs are discounted at 3.5%	Costs and QALYs are discounted at 3.5%	NR - Not updated from TA472	Costs and QALYs are discounted at 3.5%	Costs and QALYs are discounted at 3.5%	Costs and QALYs are discounted at 3.5%	Costs and QALYs are discounted at 3.5%	Consistent with NICE reference case.

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Source of utilities	Published literature (Wild et al. 2006)	GO29781 trial	Published literature (Wild et al. 2006)	AUGMENT trial	Published literature (Pettengell et al. who report the same data as Wild et al. 2006)	Published literature (Wild et al. 2006)	EPCORE NHL-1 trial, HMRN and published literature (Wild et al. 2006)	EQ-5D-3L data were collected in EPCORE NHL-1 and used to derive utility health states within the model, in line with the NICE reference case. Utility data was supplemented with values from published literature where required.
Source of costs	MIMS, eMIT, NHS reference costs (2019/2020)	eMIT, BNF, NHS reference costs (2019/2020), PSSRU 2021	NR	MIMS, eMIT, NHS reference costs (2017/2018), PSSRU 2018, published literature and previous TAs	MIMS, eMIT, NHS reference costs (2016/2017), PSSRU 2017	NHS reference costs (2004), TOPS FU303	eMIT, BNF, NHS reference costs (2023/2024), PSSRU 2022 and prior NICE TAs	Consistent with NICE reference case.
Health effect measures	Expressed in QALYs	Expressed in QALYs	Expressed in QALYs	Expressed in QALYs	Expressed in QALYs	Expressed in QALYs	Expressed in QALYs	Consistent with NICE reference case.

[†] TA629 is an update from TA472, for which the committee papers are not available on the NICE website. There are limited details around methodology in the TA629 publication.
BNF, British National Formulary; eMIT, drugs and pharmaceuticals electronic market information tool; FL, follicular lymphoma; MIMS, Monthly Index of Medical Specialties; NHS, National Health Service, NR, not reported; PSSRU, Personal Social Services Research Unit; QALY, quality-adjusted life year; TA, technology appraisal

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3.2.3 Intervention technology and comparators

3.2.3.1 Intervention

As described in Section 1.1, the intervention of interest in this analysis is epcoritamab. Epcoritamab is administered through subcutaneous injection according to the dosing regimen for the optimisation part of the EPCORE NHL-1 trial. This regimen consists of a priming dose of 0.16 mg, intermediate doses of 0.80 and 3.00 mg, and a full dose of 48.0 mg until unacceptable toxicity, disease progression, or withdrawal of consent. The epcoritamab dosing regimen applied within the model is presented in Table 45.

Table 45. Epcoritamab dosing regimen applied in the model

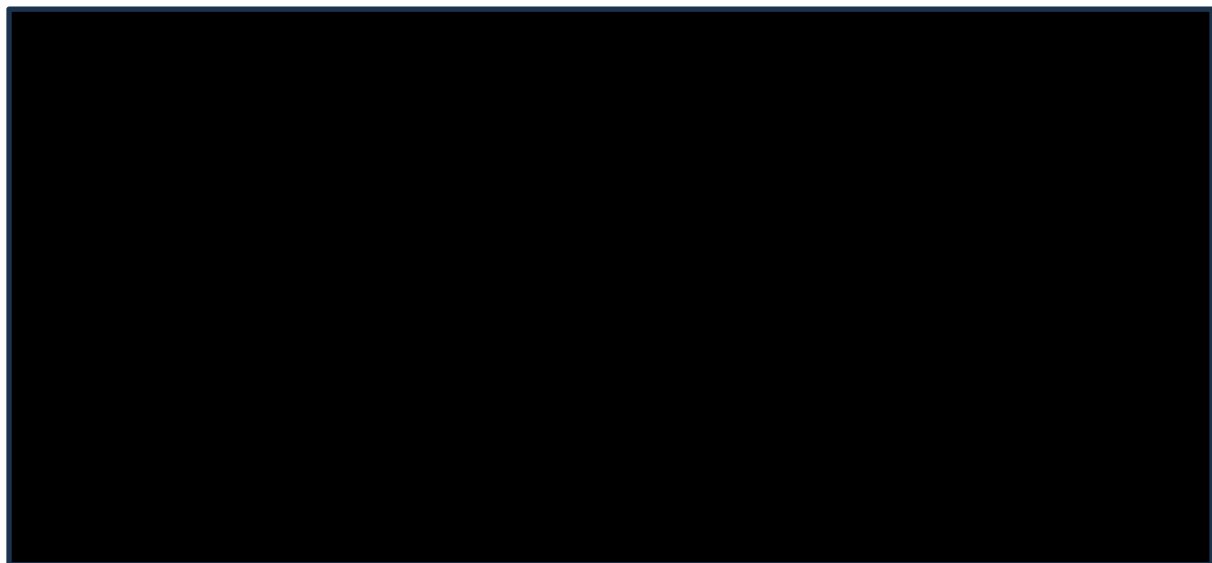
Dose	Administration Frequency
0.16 mg	One administration on day 1 of cycle 1 (28-day cycle)
0.80 mg	One administration on day 8 of cycle 1 (28-day cycle)
3.00 mg	One administration on day 15 of cycle 1 (28-day cycle)
48.0 mg	Once weekly from day 22 of cycle 1 (28-day cycle) until cycle 3 Once every two weeks for cycle 4 to 9 Once every four weeks from cycle 10 and beyond

At a median of 5.7 (0.4 – 11.8) months study follow-up in Arm A of the dose optimisation part of EPCORE NHL-1, the optimisation cohort was considered adequate to assess any impact of the three step-up dose regimen (including 3.00 mg) on response rates, since the duration of follow-up includes the first scheduled imaging assessments. As is detailed in regulatory documentation to the European Medicines Agency, the response rates in the optimisation cohort using the three step-up dose regimen are similar to those in the expansion cohort using the two step-up dose regimen.⁹⁶ Further, pharmacokinetic outcomes are similar between patients who received the three step-up dose regimen and patients who received the two step-up dose regimen in EPCORE NHL-1.⁷ Therefore, the clinical efficacy outcomes from the expansion cohort presented in Section 2 are considered suitable with sufficiently long follow-up for use within the economic evaluation.

3.2.3.2 Comparators

As outlined in Section 2.12.1.2, the comparator for this appraisal is a basket of current 4L+ care therapies to recognise that there is no standardised treatment pathway for FL as patients move to later lines of treatment. Therefore, this evaluation considers the cost of current 4L+ care through a weighted basket of therapies identified as relevant for patients with 4L+ R/R FL according to HMRN as presented in Figure 22.⁵

Figure 22. Approach to modelling the current 4L+ care basket using HMRN data



OB is selected as the most appropriate therapy for costing the 'Other + experimental' sub-basket as it is the therapy option most reflective of UK practice as described by clinical experts.⁹
Source: HMRN⁵



Outcomes data for the comparator arm in this appraisal were also sourced from the HMRN data set to best reflect outcomes observed in UK clinical practice. Outcomes were compared with epcoritamab in the MAIC (described in Section 2.12) with the output being used within the economic evaluation.

3.3 Clinical parameters and variables

3.3.1 Evidence synthesis

Evidence to describe the characteristics of the patient population and the effectiveness of epcoritamab was primarily derived from the EPCORE NHL-1 trial, an open label, multicentre, phase 1/2 trial in participants aged 18 years or older with

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relapsed, progressive and/or refractory disease. The trial contains an escalation part, an expansion part and an optimisation part, with the expansion part of the study being used to model the clinical efficacy of epcoritamab within this economic evaluation. As EPCORE NHL-1 was a single-arm trial, an SLR was performed to source efficacy data for current 4L+ options in clinical practice. The SLR did not identify any data sources that reported outcomes in UK patients with 4L+ R/R FL who received treatments that resemble UK clinical practice. Therefore, an ITC using data obtained from HMRN was conducted to derive comparator survival and response data as described in Section 2.12.

3.3.2 Survival analysis

As described in Section 3.2.2, the proportion of patients in the PFS, PD, and Death health states at each cycle in the model is determined by PFS and OS curves using data from the dose expansion part of EPCORE NHL-1. As this evaluation compares the outcomes for epcoritamab with current 4L+ care over a lifetime horizon, longer than the follow-up duration available from EPCORE NHL-1 and HMRN, the observed PFS and OS curves required extrapolation. In line with the data presented in Section 2.8, these analyses consider COVID-modified outcomes from EPCORE NHL-1.

3.3.2.1 Assessing the proportional hazards assumption

The proportional hazards assumption (PHA) was assessed using the epcoritamab survival curves presented in Section 2 to determine whether a constant hazard ratio (HR) could be applied to the epcoritamab curve to extrapolate long-term outcomes for HMRN, or whether alternative methods should be considered. Three assessments were conducted:

- Visual inspection of log-cumulative hazards against log-time. Approximately, parallel lines indicate the PHA holds, while non-parallel or crossing lines suggest it does not.
- Visual inspection of Schoenfeld residuals. These residuals reflect the difference between observed covariates and expected value over time, with a plot centred around zero and showing no trend supporting the PHA.

- The Grambsch and Therneau test. This evaluates the relationship between Schoenfeld residuals and survival time, with a significant p-value ($p < 0.05$) indicating a violation of the PHA.

The results of all tests described in Table 46 indicate that the PHA is likely to hold for both OS and PFS; therefore, in line with the guidance within TSD14, applying constant HRs is suitable in all cases for long-term extrapolations.⁷² This approach also reduces the number of estimated degrees of freedom compared with using independent models, thereby enhancing the precision of the long-term survival estimates. Further details around the assessment of proportional hazards are presented in Appendix J.

Table 46. Assessing the PHA for epcoritamab compared with HMRN

Scenario	Outcome	Log-cumulative hazard plots	Schoenfeld residuals plot [†]	Grambsch-Therneau test [‡]	PHA violated?	HR applied	p-value
Epcoritamab vs Current 4L+ Care	OS	██████	██████████	██████	No	████	██████
	PFS	██████	██████████	██████	No	████	██████

[†] If p-value > 0.05, no evidence to reject PHA

[‡] If the covariate is time-independent, no evidence to reject PHA

HMRN, Haematological Malignancy Research Network; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; PHA, proportional hazards assumption

3.3.2.2 Extrapolation of survival outcomes

To extrapolate survival outcomes over the lifetime horizon, standard parametric curves (exponential, gamma, generalised gamma, Gompertz, log-normal, log-logistic, and Weibull) were fitted to the PFS OS, and TTD curves as per NICE TSD14.⁷²

Curve selection was performed according to the following criteria presented in TSD14, namely:

- Akaike's Information Criterion (AIC) and the Bayesian Information Criterion (BIC) were used to test the relative fit of each parametric model, while also penalising overfitting. Models with an AIC or BIC difference of ≤ 2 were considered statistically comparable.⁹⁷

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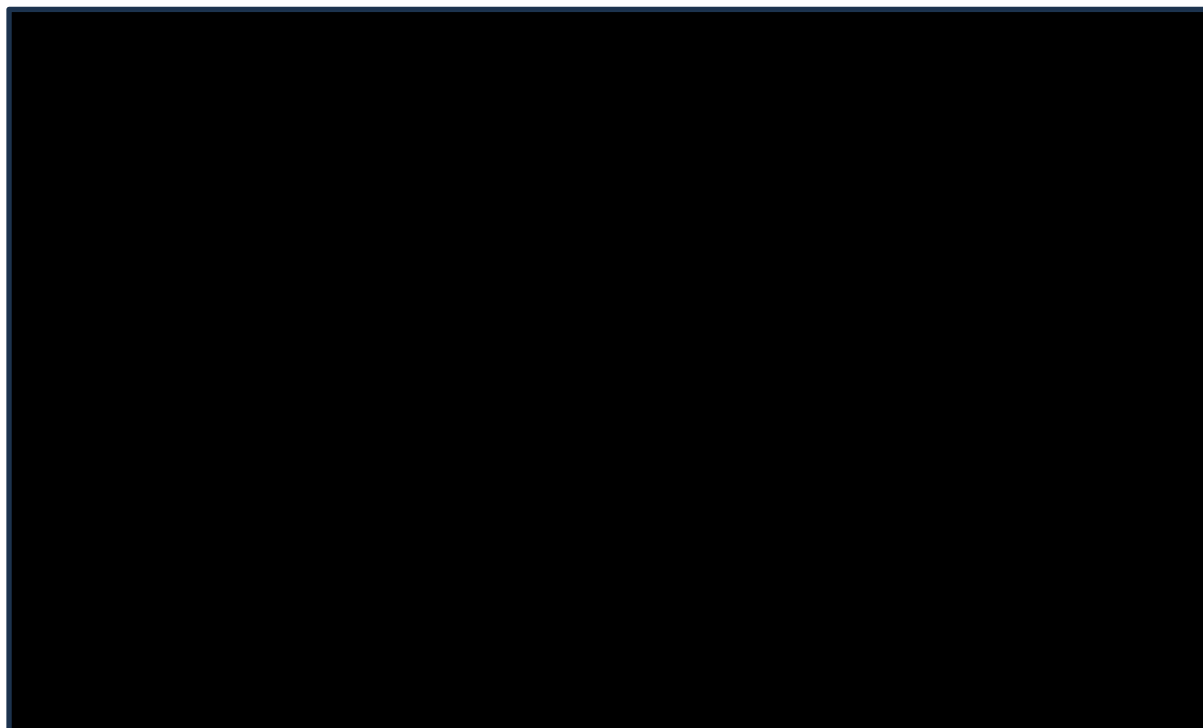
- Each curve was visually compared against the KM data to evaluate the fit. Parametric distributions that deviated substantially or produced implausible projections were discounted.
- The chosen distributions were compared with landmark survival estimates obtained during individual consultations with UK clinical experts from centres around the country and experienced in using bispecific antibodies for treating FL. Six engagements had taken place. In five of these engagements, the clinicians were able to provide landmark survival estimates at specified timepoints in order to guide the most appropriate model selection. Some clinical experts were not able to provide landmark estimates for all outcomes due to time constraints for the engagements.

In the base-case analysis, PFS and OS outcomes for current 4L+ care are derived by applying the MAIC-adjusted hazard ratios (HRs) to the unadjusted epcoritamab data, ensuring comparability between treatment arms in an EPCORE NHL-1 trial population.

3.3.2.3 Overall survival

Parametric distributions were applied to the observed OS data from EPCORE NHL-1 using the methodology described in Section 3.3.2.2. As observed in Figure 23, all distributions fit well to the observed KM curve and remained within the 95% confidence interval.

Figure 23. Parametric distributions fit to the observed epcoritamab OS data from EPCORE NHL-1



Cut-off date: [REDACTED], Median follow-up = [REDACTED], N=81
OS, overall survival

Based on the AIC and BIC values (Table 47), the exponential distribution provided the best statistical fit to the observed data. However, the log-normal, log-logistic, Weibull, gamma, and Gompertz distributions also demonstrated acceptable fits in terms of AIC. The generalised gamma distribution is less comparable as the AIC and BIC are >2 higher than the exponential model.

Table 47. AIC and BIC values of standard parametric distributions fit to epcoritamab OS data

Distribution	AIC	BIC
Exponential	[REDACTED]	[REDACTED]
Log-normal	[REDACTED]	[REDACTED]
Log-logistic	[REDACTED]	[REDACTED]
Weibull	[REDACTED]	[REDACTED]
Gamma	[REDACTED]	[REDACTED]
Gompertz	[REDACTED]	[REDACTED]
Generalised gamma	[REDACTED]	[REDACTED]

Cut-off date: [REDACTED], Median follow-up = [REDACTED] months, N=81

Best-fitting distributions are in green font color

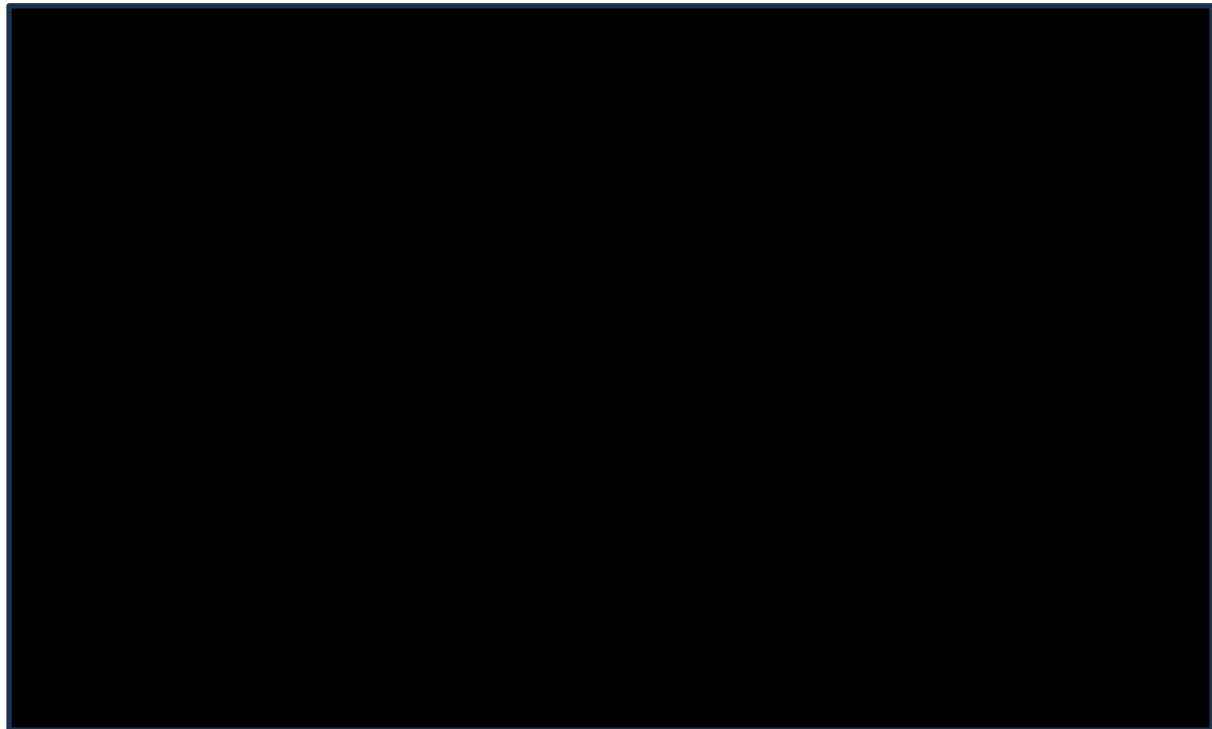
Values shaded in green denote AIC/BIC values that are ≤ 2 from the best-fitting distribution

AIC, Akaike information criterion; BIC, Bayesian information criterion; OS, overall survival

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These model fits were extrapolated to the lifetime horizon to estimate long-term OS, as illustrated in Figure 24.

Figure 24. Parametric distributions applied to epcoritamab OS data from EPCORE NHL-1 across a lifetime horizon



Cut-off date: [REDACTED], Median follow-up = [REDACTED] months, N=81
OS, overall survival

The long-term OS predictions varied across distributions. The generalised gamma model generated the most optimistic survival estimates, while the exponential, Weibull, and gamma models produced the most pessimistic outcomes. The remaining distributions estimated survival outcomes that fell between the exponential and generalised gamma distribution. These results are further supported by the landmark survival estimates found in Table 48.

Table 48. Landmark estimates of long-term survival for epcoritamab OS data from EPCORE NHL-1

Distribution	Median (months)	24 months	48 months	60 months	120 months
Observed (95% CI)	██████████	██████████	██	██	██
Exponential	██	██	██	██	██
Gamma	██	██	██	██	██
Generalised gamma	██	██	██	██	██
Log-logistic	██	██	██	██	██
Log-normal	██	██	██	██	██
Weibull	██	██	██	██	██
Gompertz	██	██	██	██	██

Cut-off date: ██████████, Median follow-up = █████ months, N=81
Values highlighted in green indicate best statistical fits (AIC and BIC) to OS data
CI, confidence interval; NR, not reached; OS, overall survival

In separate clinical validation exercises, four UK clinical experts were asked to predict long-term estimates of OS for patients treated with epcoritamab. The mean values of the estimates provided by the four clinical experts are presented in Table 49.

Table 49. Clinician estimates of long-term OS for patients treated with epcoritamab

	Lower plausible limit	Most likely value	Upper plausible limit
2 years	██	██	██
5 years	██	██	██
10 years	██	██	██
15 years	██	██	██

Estimates based on individual interviews with UK clinical experts
OS, overall survival

Among the models, the log-normal distribution had the second lowest AIC and BIC, providing a reasonable fit to the EPCORE NHL-1 data, and yielded long-term OS extrapolations consistent with clinical estimates, whereas the exponential distribution, which had the lowest AIC and BIC, is overly pessimistic compared with clinician estimates.

Considering all (visual, statistical and clinical) data available, the log-normal distribution is considered the most appropriate for extrapolating OS in the base case analysis as it provides a close fit to the observed Kaplan-Meier data and produces

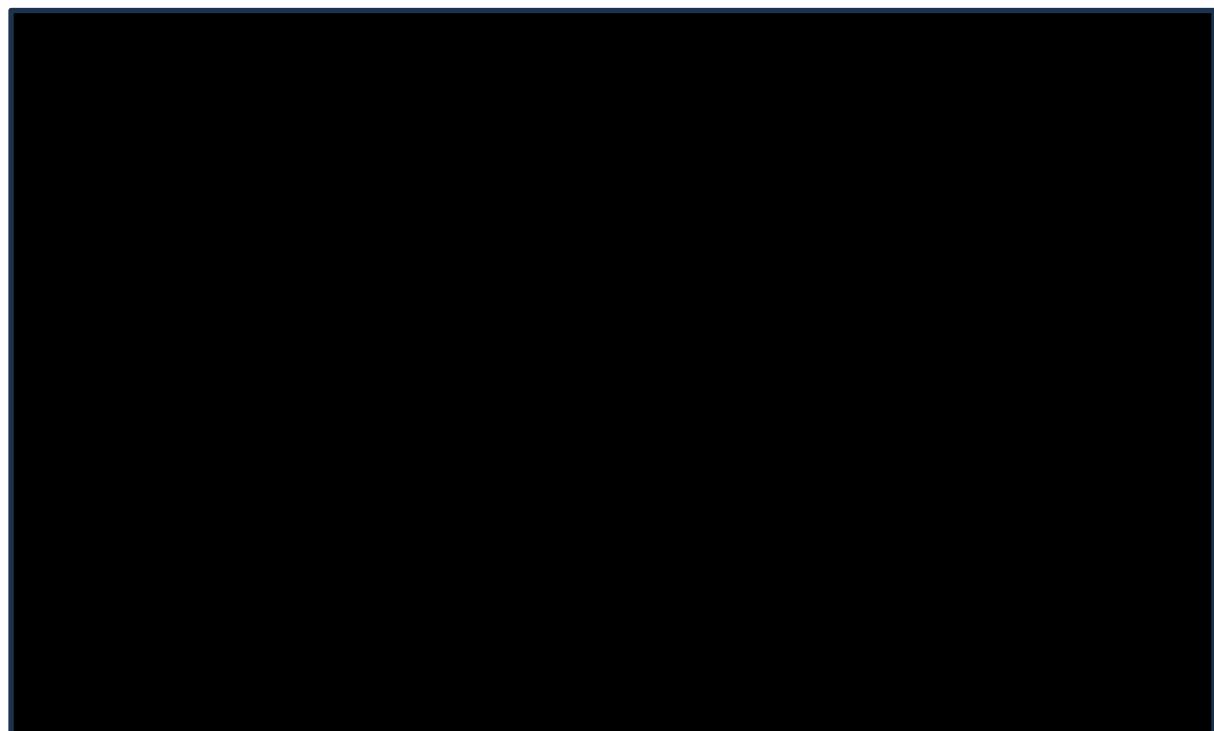
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clinically plausible long-term outcomes that are aligned with estimates provided by clinical experts.

3.3.2.4 Progression-free survival

Parametric distributions were applied to the observed PFS data from EPCORE NHL-1 using the methodology described in Section 3.3.2.2. As observed in Figure 25, the Gompertz and generalised gamma distributions followed the observed data most closely, with the latter remaining within the 95% confidence interval for the entire observed period. While the Gompertz distribution predicted an almost plateauing PFS, the generalised gamma distribution offered a more clinically plausible projection.

Figure 25. Parametric distributions fit to the observed epcoritamab PFS data from EPCORE NHL-1



Cut-off date: [REDACTED] Median follow-up = [REDACTED] months, n=81
PFS, progression-free survival

Based on AIC and BIC values (Table 50), the generalised gamma distribution provided the best fit to the observed data. In contrast, all other distributions had a >5 difference in AIC/BIC compared with generalised gamma, indicating they were statistically less comparable.

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Table 50. AIC and BIC values of standard parametric distributions fit to epcoritamab PFS data

Distribution	AIC	BIC
Generalised gamma		
Gompertz		
Log-normal		
Log-logistic		
Weibull		
Gamma		
Exponential		

Cut-off date: , Median follow-up = months, N=81

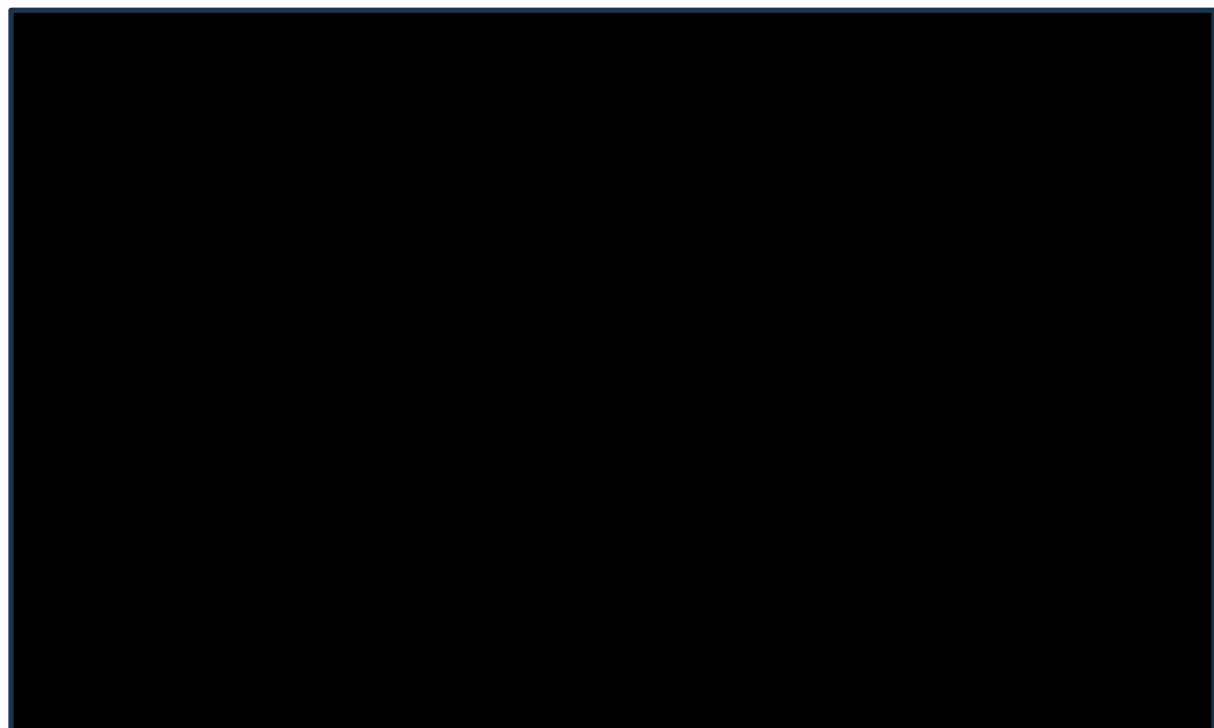
Best-fitting distributions are in green font color

Values shaded in green denote AIC/BIC values that are ≤ 2 from the best-fitting distribution

AIC, Akaike information criterion; BIC, Bayesian information criterion; PFS, progression-free survival

Whereas the Gompertz distribution predicts optimistic long-term survival outcomes, the exponential, gamma and Weibull models were more pessimistic. The log-logistic and log-normal distributions fell between these extremes (Figure 26).

Figure 26. Parametric distributions applied to epcoritamab PFS data from EPCORE NHL-1 across a lifetime horizon



Cut-off date: , Median follow-up = months, n=81

PFS, progression free survival

The estimated 24-month survival of all distributions lies within the 95% confidence interval of the observed trial data, as shown in Table 51. The survival estimates

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generated from the Gompertz distribution have a minimal decline over time; thus, these estimates may be less clinically plausible. The generalised gamma distribution provides a comparable survival estimate at 24 months.

Table 51. Landmark estimates of long-term survival for epcoritamab PFS data from EPCORE NHL-1

Distribution	Median (months)	24 months	48 months	60 months	120 months
Observed (95% CI)	██████████	██████████	██	██	██
Exponential	██	██	██	██	██
Gamma	██	██	██	██	██
Generalised gamma	██	██	██	██	██
Gompertz	██	██	██	██	██
Log-logistic	██	██	██	██	██
Log-normal	██	██	██	██	██
Weibull	██	██	██	██	██

Cut-off date: ████████, Median follow-up = █████ months, N=81
Values highlighted in green denote the best fitting distributions
CI, confidence interval; NR, not reached; PFS, progression free survival

In separate clinical validation exercises, clinicians were asked to predict long-term estimates of PFS for patients treated with epcoritamab. The mean values of the estimates provided by the four clinical experts are presented in Table 52.

Table 52. Clinician estimates of long-term PFS for patients treated with epcoritamab

	Lower plausible limit	Most likely value	Upper plausible limit
2 years	██	██	██
4 years	██	██	██
5 years	██	██	██
10 years	██	██	██

Estimates based on individual interviews with UK clinical experts
PFS, progression free survival

From the results of the statistical fit, the generalised gamma distribution had the best-fitting AIC and BIC. The Gompertz and log-normal distributions had the second-best and third-best fitting distributions with respect to AIC and BIC. When assessing the long-term extrapolations of the distribution, the Gompertz distribution predicted an almost plateauing survival for epcoritamab PFS, which may be clinically implausible. Landmark estimates of the generalised gamma distribution were

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comparable at 24 months and fit well to observed data; however, the long-term outcomes of the generalised gamma distribution only matched the upper plausible limit of clinical expert opinion. Thus, in full consideration of the available evidence, the log-normal distribution is selected as a more conservative and clinically plausible choice, balancing reasonable statistical fit with alignment to clinical expert opinion.

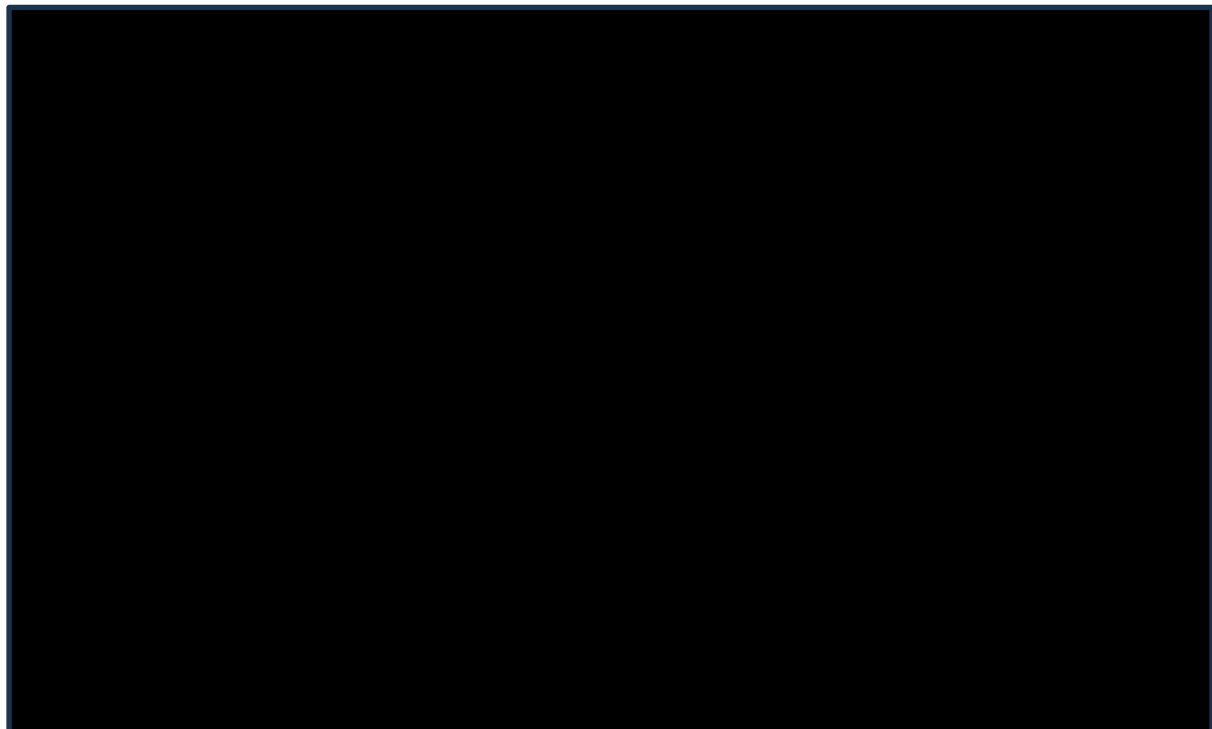
3.3.2.5 Time to treatment discontinuation

3.3.2.5.1 Epcoritamab

As for OS and PFS, parametric distributions were applied to the observed TTD data from EPCORE NHL-1 using the methodology described in Section 3.3.2.2. As observed in Figure 27, all fitted distributions follow the data well and fell within the 95% confidence interval estimates of survival.

It is noteworthy that the PFS and TTD curves from EPCORE NHL-1 meet within the first 6 months, with the TTD curve briefly being slightly above the PFS curve. This may be caused by different factors, such as the PFS curve being heavily censored during the initial months of the trial and, with PFS being censored at the last PFS measurement, the date of last PFS measurement may be earlier than the date of discontinuation. Additionally, clinicians may not halt treatment for patients immediately after progression or there may be a difference between investigator and IRC-assessed progression, resulting in the patients receiving treatment longer than the IRC-assessed progression date. However, after ~6 months TTD falls below PFS as expected.

Figure 27. Parametric distributions fit to the observed epcoritamab TTD data from EPCORE NHL-1



Cut-off date: [REDACTED], Median follow-up = [REDACTED] months, N=81
TTD, time to treatment discontinuation

Based on AIC and BIC values, the log-normal and exponential distributions appeared to be the best fitting distributions (Table 53). With regards to AIC, only generalised gamma was comparable to the log-normal and exponential distributions, whereas for BIC, no other distributions were comparable.

Table 53. AIC and BIC values of standard parametric distributions fit to epcoritamab TTD data

Distribution	AIC	BIC
Log-normal	[REDACTED]	[REDACTED]
Exponential	[REDACTED]	[REDACTED]
Generalised gamma	[REDACTED]	[REDACTED]
Log-logistic	[REDACTED]	[REDACTED]
Weibull	[REDACTED]	[REDACTED]
Gompertz	[REDACTED]	[REDACTED]
Gamma	[REDACTED]	[REDACTED]

Cut-off date: [REDACTED], Median follow-up = [REDACTED] months, N=81

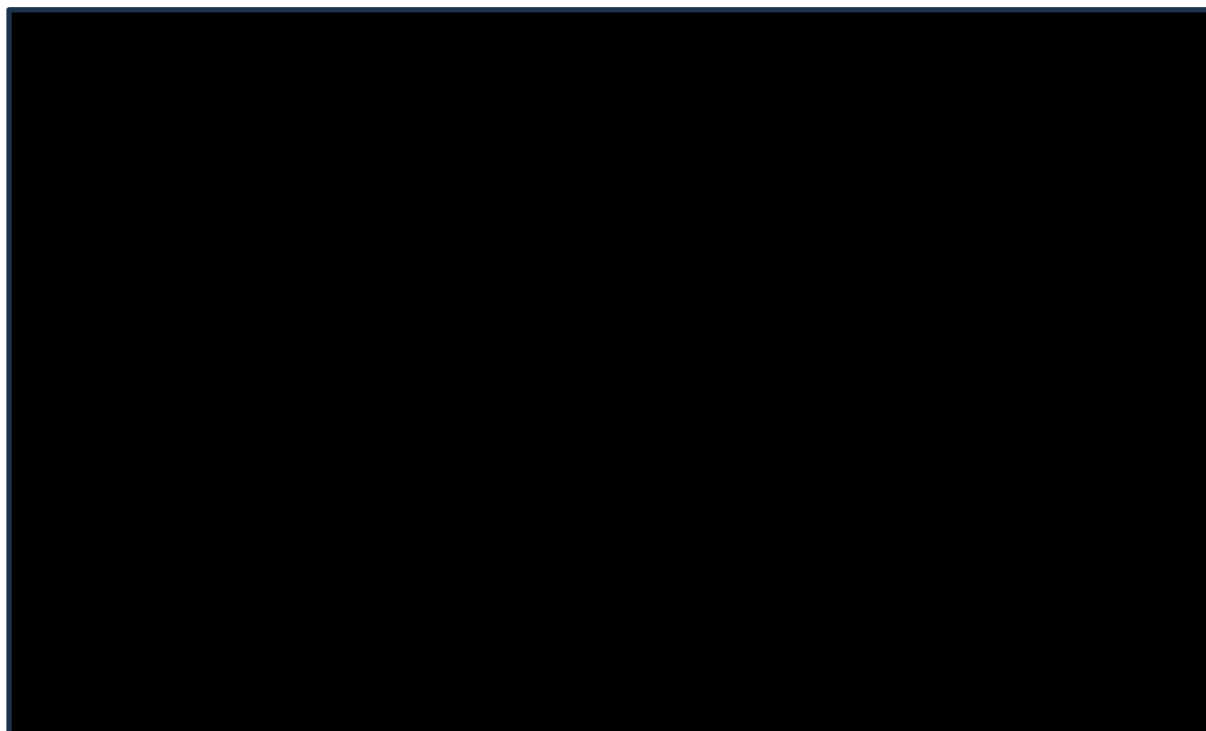
Best-fitting distributions are in green font color

Values shaded in green denote AIC/BIC values that are ≤ 2 from the best-fitting distribution

AIC, Akaike information criterion; BIC, Bayesian information criterion; TTD, time to treatment discontinuation

These distributions were extrapolated to a lifetime horizon to estimate long-term TTD, as illustrated in Figure 28.

Figure 28. Parametric distributions applied to epcoritamab TTD data from EPCORE NHL-1 across a lifetime horizon



Cut-off date: [REDACTED], Median follow-up = [REDACTED] months, N=81
TTD, time to treatment discontinuation

The exponential, gamma, and Weibull distributions have comparable, conservative long-term time to treatment discontinuation estimates, whereas long-term estimates produced by the generalised gamma and log-logistic distributions are the most optimistic. The remaining distributions (log-normal and Gompertz) predict a long-term TTD that falls between the most conservative and most optimistic distribution. These findings are reflected by the landmark estimates in Table 54.

Table 54. Landmark estimates of long-term survival for epcoritamab TTD data from EPCORE NHL-1

Distribution	Median (months)	24 months	48 months	60 months	120 months
Observed (95% CI)					
Exponential					
Gamma					
Generalised gamma					
Gompertz					
Log-logistic					
Log-normal					
Weibull					

Cut-off date: , Median follow-up = months, N=81
Values highlighted in green denote the best-fitting distributions
CI, confidence interval; NR, not reached; TTD, time to treatment discontinuation

As described previously, AbbVie held separate clinical validation exercises with UK experts to predict and validate long-term estimates of TTD for patients treated with epcoritamab. The mean values of the estimates provided by the clinical experts are presented in Table 55.

Table 55. Clinician estimates of long-term TTD for patients treated with epcoritamab

	Lower plausible limit	Most likely value	Upper plausible limit
2 years			
4 years			
5 years			
10 years			

Estimates based on individual interviews with UK clinical experts
TTD, time to treatment discontinuation

The log-normal distribution demonstrated the best fit to the observed data, capturing the shape of the Kaplan-Meier curve and providing the lowest AIC and comparable BIC values. While the long-term extrapolation from the log-normal distribution slightly overestimates the proportion of patients remaining on treatment at 5 and 10 years compared to clinical expert opinion, the differences are small and fall well within the clinically plausible range. Notably, the observed data point at 2 years falls below the corresponding landmark estimate from clinical opinion, however it is still within the lower plausible limit. Given the maturity of the observed TTD data and the strong statistical fit, the log-normal distribution was applied within the base case analysis.

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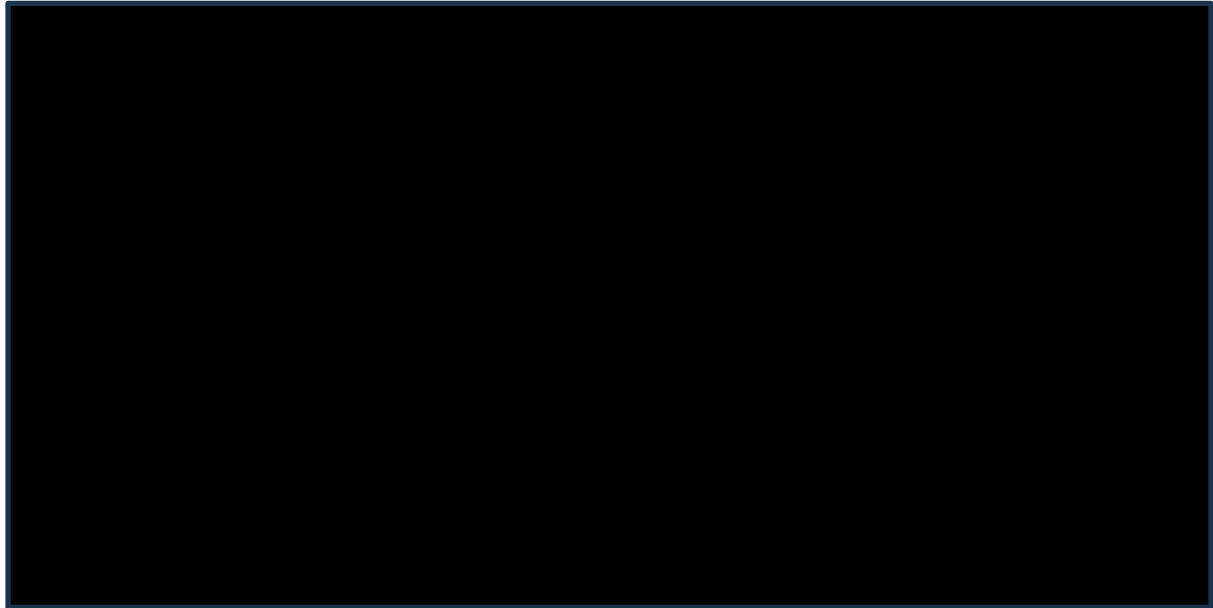
This approach represents a conservative assumption, as further alignment with clinical expectations would support the use of alternative distributions with shorter treatment durations and lower overall treatment costs for epcoritamab.

3.3.2.5.1.1 Maximal treatment duration for complete responders

During engagements on TTD for epcoritamab, clinical experts noted that patients with a CR would be unlikely to continue receiving treatment beyond two years. This can be seen in the EPCORE NHL-1 trial, whereby █ patients (█%) with a CR remain on treatment at a median follow-up of █ months. By three years, very few patients with a CR would continue to receive epcoritamab in practice. Clinical experts noted that patient preference, management of adverse events, and experience with bispecific antibodies in other B-cell lymphoma subtypes would influence their decision-making at these time points.

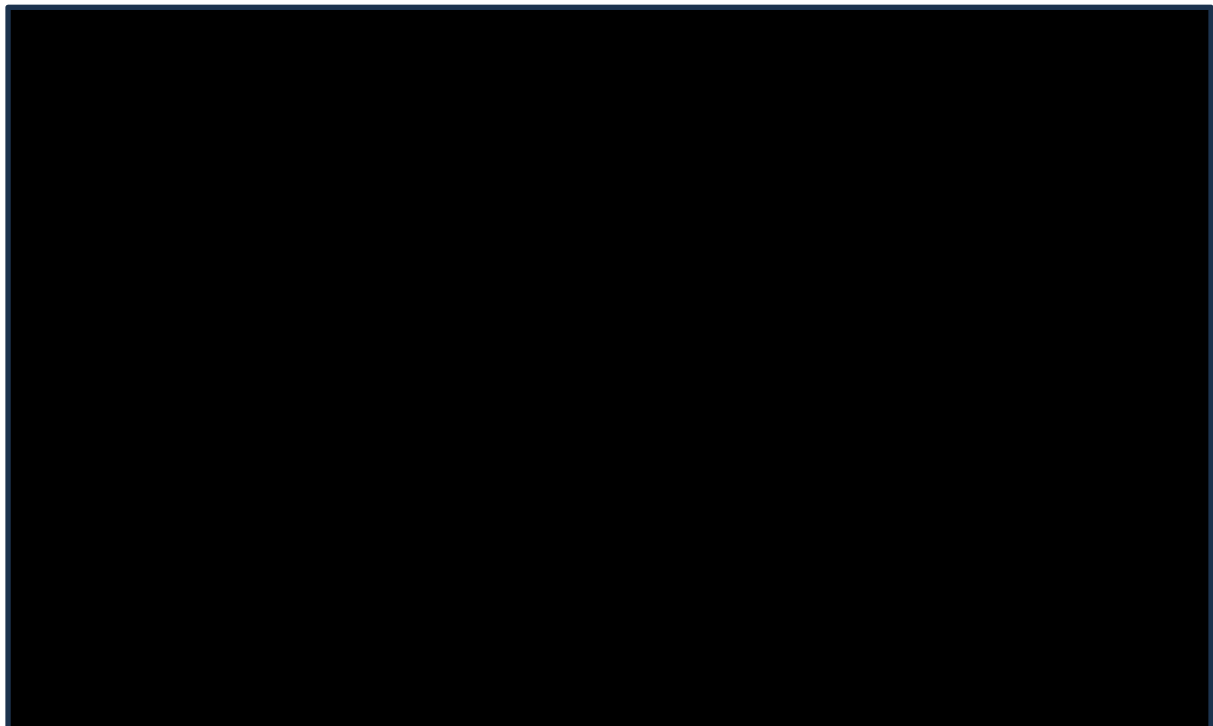
Data from the EPCORE NHL-1 trial showed that all patients with 4L+ FL remaining on treatment after 15 months are complete responders (Figure 29). Indeed, survival for patients with a CR is durable and OS at three years was shown to be close to █% (Figure 30). Further analysis has demonstrated that patients who achieve a CR, but stop treatment due to reasons other than progression or death (n = █), are likely to maintain their CR, as evidenced by the flat PFS curve within a year of subsequent follow-up (█% PFS at 6 months and 12 months respectively) (Figure 31). This set of results aligns with clinical expectations and experiences with bispecific antibodies in other B-cell lymphoma subtypes. As such, the base case analysis for this appraisal assumes that epcoritamab treatment costs are no longer accrued for complete responders after three years. The impact of this is assessed within the sensitivity analyses (Section 3.11.3.2).

Figure 29. Kaplan-Meier Plot of Progression-Free Survival by Best Overall Response Based on IRC Assessment, Lugano Criteria



Data cut off [REDACTED], assessed by independent review committee
CI, confidence interval; CR, complete response; PR, partial response

Figure 30. Kaplan-Meier Plot of Overall Survival by Best Overall Response Based on IRC Assessment, Lugano Criteria



Data cut off [REDACTED], assessed by independent review committee
CI, confidence interval; CR, complete response; PR, partial response

Figure 31. Kaplan-Meier Plot of PFS in patients who achieved CR and discontinued treatment while progression-free and alive

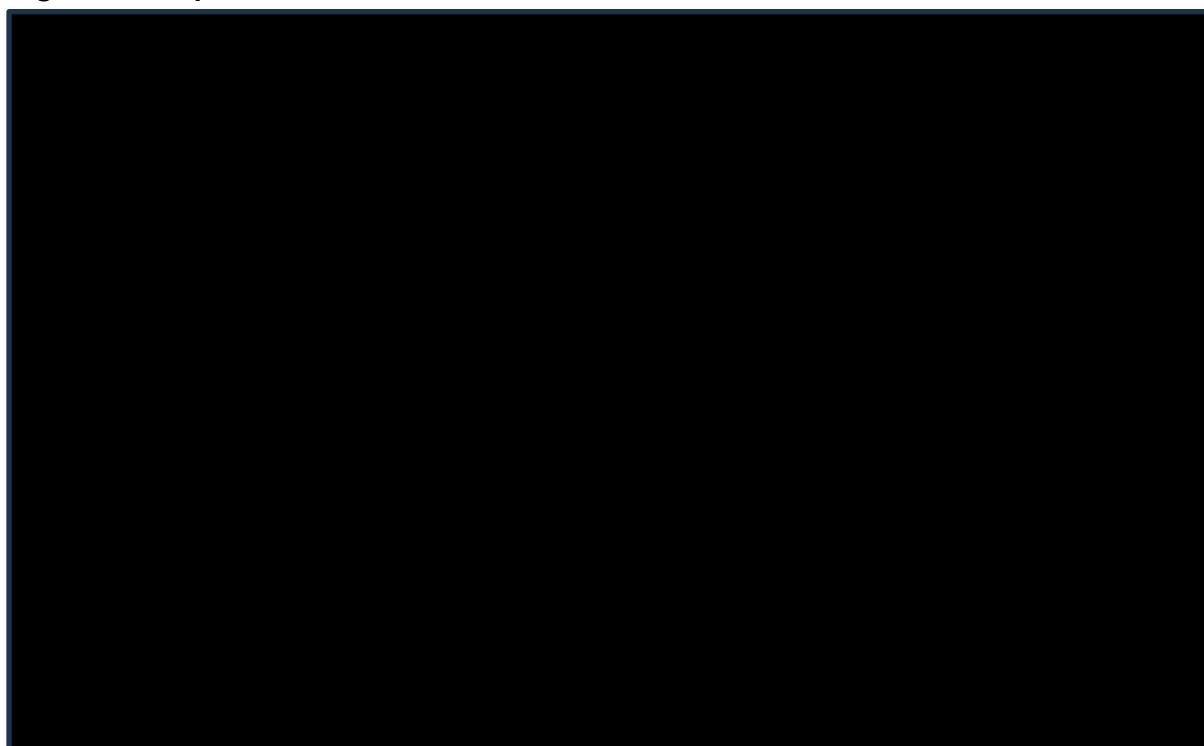


Data cut off [REDACTED]
CR, complete response; PFS, progression-free survival

3.3.2.5.2 Current 4L+ care

Unlike for PFS and OS, it is not appropriate to use a MAIC-derived HR to derive TTD for current 4L+ care because the HMRN treatment basket consists of multiple therapies with different fixed treatment durations, making direct comparisons with the trial treatment less meaningful. Instead, raw HMRN TTD data was used to model patient discontinuation from current 4L+ care. This directly reflects observed treatment discontinuation patterns in UK clinical practice, without relying on the use of hazard ratios. Given that the HMRN treatment basket includes therapies with fixed treatment durations, using raw HMRN TTD allows assessment of how these variations impact cost-effectiveness outcomes. The raw HMRN TTD data are presented in Figure 32.

Figure 32. Kaplan-Meier curve for HMRN TTD data



HMRN, Haematological Malignancy Research Network; TTD, time to treatment discontinuation

Parametric distributions were applied to the TTD data from HMRN using the methodology described in Section 3.3.2.2. Based on AIC and BIC, the exponential distribution was the best-fitting distribution (Table 56). Gamma, Gompertz, and Weibull distributions had a comparable AIC, whilst none were comparable when considering BIC.

Table 56. AIC and BIC values of standard parametric distributions fit to HMRN TTD data

Distribution	AIC	BIC
Exponential	■	■
Gamma	■	■
Generalised gamma	■	■
Gompertz	■	■
Log-logistic	■	■
Log-normal	■	■
Weibull	■	■

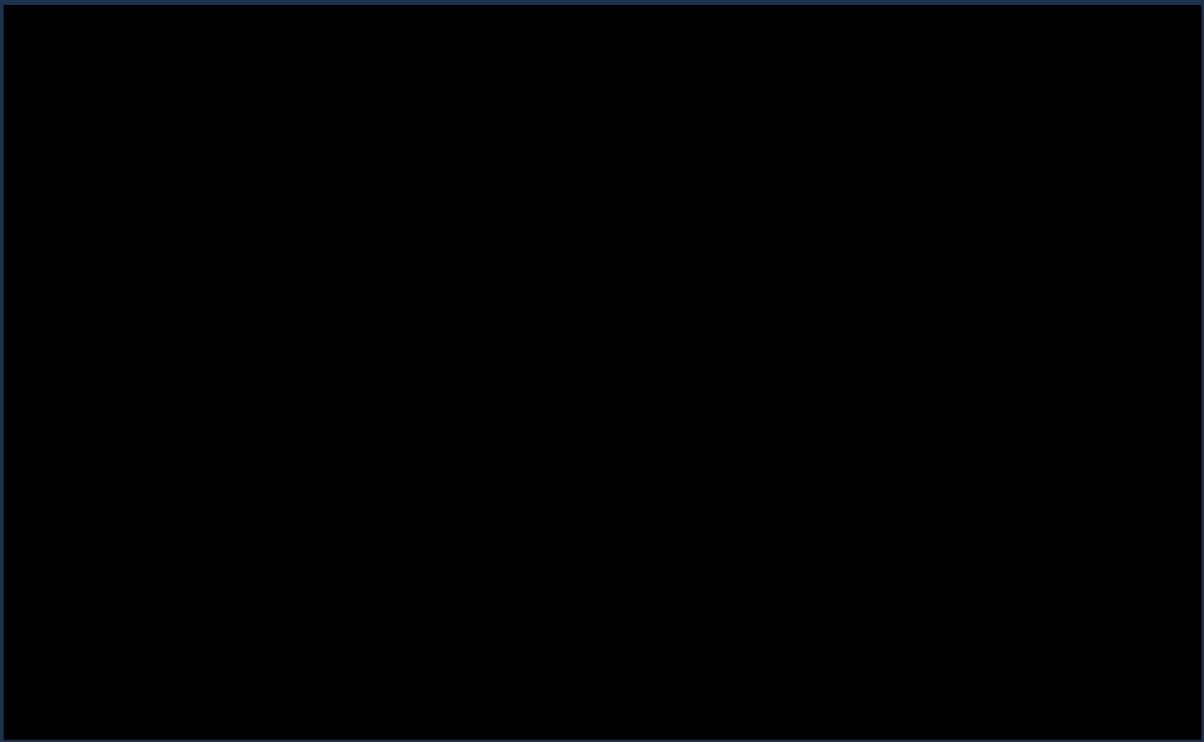
Best-fitting distributions are in green font colour

Values shaded in green denote AIC/BIC values that are ≤ 2 from the best-fitting distribution

AIC, Akaike information criterion; BIC, Bayesian information criterion; HMRN, Haematological Malignancy Research Network; TTD, time to treatment discontinuation

As observed in Figure 33, long-term estimates from most models were comparable due to the maturity of the data, though estimates produced by the log-logistic and log-normal distribution were marginally the most optimistic.

Figure 33. Long-term extrapolation of long-term current 4L+ care TTD data



TTD, time to treatment discontinuation

Table 57 shows that landmark model estimates were largely comparable and median estimates predicted by all distributions fall within the 95% confidence interval of the observed data.

Table 57. Long-term current 4L+ care TTD survival estimates at landmark timepoints

Distribution	Median (months)	24 months (%)	48 months (%)	60 months (%)	120 months (%)
Observed (CI)					
Exponential					
Gamma					
Generalized gamma					
Gompertz					
Log-logistic					
Log-normal					
Weibull					

CI, confidence interval; TTD, time to treatment discontinuation

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Based on the best statistical fit and the reasonable extrapolations and landmark estimates, the exponential distribution is recommended to model HMRN TTD data, and therefore, discontinuation of current 4L+ care.

3.3.3 Adverse events

The adverse events observed in patients treated with epcoritamab are outlined in Section 2.13. To reflect the impact of AEs, the costs and HCRU associated with AE management are included within the economic evaluation. The model accounted for the inclusion of Grade 3 or 4 TEAEs that occurred in $\geq 5\%$ of the patients sourced from the EPCORE-NHL-1 Dose Expansion 4L+ cohort (N=81) and the comparator studies detailed in TA894 (Table 58).⁷ The limited available data reporting AE outcomes for chemotherapy limits the ability to model safety outcomes using a basket approach. Therefore, since R-Chemo was the second largest sub-basket in current 4L+ care, data for R-CHOP from TA894 were used in this analysis.¹⁹ For AEs that were not reported, it was assumed that the probability of the AEs is 0.

Table 58. Proportion of patients with TEAEs for each treatment

Grade 3 or 4 TEAEs occurring in $>5\%$ of patients	Epcoritamab (EPCORE NHL-1 Expansion part – 4L+ cohort)	Current 4L+ care
Anaemia	■	4.50%
COVID-19	■	0.00%
COVID-19 pneumonia	■	0.00%
Leukopenia/Leukocytopenia	■	30.80%
Lymphopenia	■	0.00%
Neutropenia	■	90.30%
Neutrophil count decreased	■	0.00%
Pneumonia	■	0.00%

TEAEs of grade 3 or above that occurred in $\geq 5\%$ of the patients in EPCORE NHL-1 or data sources reporting current 4L+ care were included in the cost-effectiveness model
NICE, National Institute for Health and Care Excellence; TA, technology appraisal; TEAEs, treatment-emergent adverse events

3.3.4 Background mortality

Estimates of the general population mortality (i.e., mortality not related to the disease) are taken from the most recent life tables reported by the Office of National Statistics (ONS) for the year 2020-2022 for England and Wales.⁹⁸ The general population mortality was adjusted by the baseline mean age and sex ratio of the EPCORE NHL-1 population.

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Background mortality is incorporated in survival extrapolations in the CEM using the internal additive hazards adopted for the epcoritamab survival extrapolations. In this approach, parametric survival fits are used to generate OS data and to calculate a cyclic hazard. Patient background mortality was determined using age- and sex-matched calculations, as previously described. The OS from the preceding cycle was then multiplied by the exponent of background mortality and the hazard of OS for the new cycle.

EPCORE NHL-1 data were fitted using the internal additive hazards approach, i.e. distinguishing between disease related hazards and background mortality using the most recent national life tables for England and Wales (2020-2022) published by the ONS.⁹⁸⁻¹⁰⁰

To incorporate the background mortality related hazards for the target population into the CEM, the internal additive hazard approach was adopted using the function presented below.⁹⁹

$$h(t) = h_{GPM}(t) + h_{DSM}(t)$$

The hazards ($h(t)$) are the sum of the general population mortality (GPM) hazards ($h_{GPM}(t)$) and disease-specific mortality (DSM) hazards estimated by a parametric distribution ($h_{DSM}(t)$).

3.4 Measurement and valuation of health effects

3.4.1 Health-related quality of life data from clinical trials

The EPCORE NHL-1 trial included assessment of HRQoL during the study, which can be used to derive utility values for modelling analysis. A standardised measure of health status, the EQ-5D-3L, was used to provide a generic measure of HRQoL.¹⁰¹

In the EPCORE NHL-1 trial, the EQ-5D-3L questionnaire was completed on day 1 of cycle 1 and repeated on day 1 of cycles 3, 5, 7 and 9, (treatment cycles consist of 28 days) and at the end of treatment. An end of treatment EQ-5D-3L assessment was provided as soon as possible, within 7 days after withdrawing from treatment (either

due to disease progression or intolerable toxicities). No further follow-up for EQ-5D-3L assessment was conducted after the end of treatment assessment.

A total of [REDACTED] complete EQ-5D-3L measurements were included in the utility analyses. Table 59 provides an overview of the number of complete EQ-5D-3L responses received at each time point per health state. As is common in clinical trials, the number of responses in PFS declined over time as patients transitioned to PD state, potentially as a result of a declining number of patients receiving treatment, loss of follow-up and survey fatigue.

Table 59. Number of responses in the FL population of GCT3013-01 trial using the [REDACTED] DCO, by time point and health state

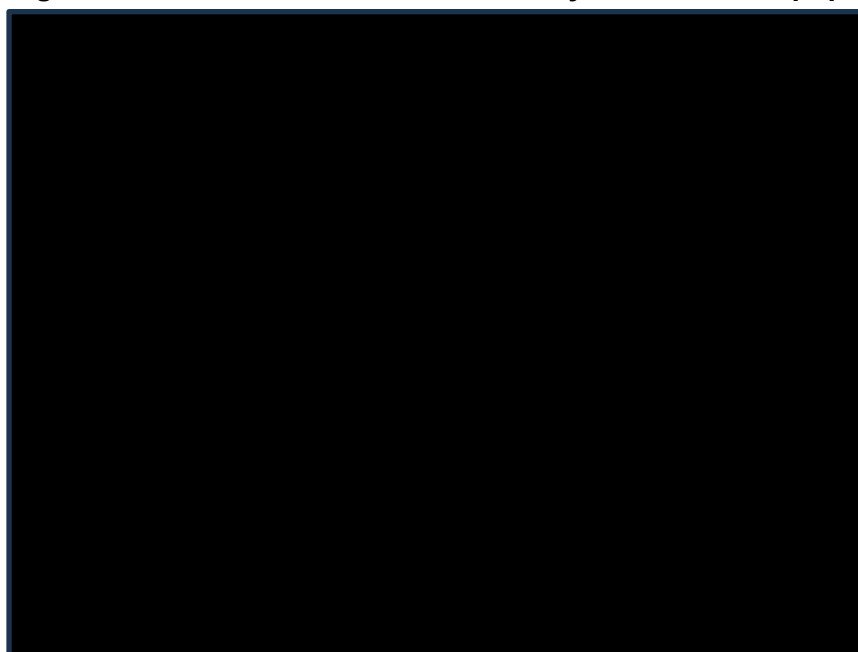
Time point	Numbers at risk*	Total observations	PFS	PD
Baseline:	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Day 1 Cycle 1	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Day 1 Cycle 3	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Day 1 Cycle 5	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Day 1 Cycle 7	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Day 1 Cycle 9	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
End of treatment	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

* Numbers of patients receiving treatment at Day 1 of cycle 1/3/5/7/9.

DCO, data cut-off; FL, follicular lymphoma; PD, progressed disease; PFS, progression-free survival.

Figure 34 is a histogram displaying the distribution of all analysed [REDACTED] observations.

Figure 34. Distribution of EQ-5D-3L utility data in the FL population of EPCORE NHL-1



Cut-off date: [REDACTED]
FL, follicular lymphoma

The descriptive analysis by health state displays a mean utility of [REDACTED] in the PFS health state and a mean utility of [REDACTED] in the PD health state. Further, the mean utility measurement at baseline (PFS) was [REDACTED], while the first utility measurement of patients in the PD state was [REDACTED], as shown in Table 60. As some patients had multiple measurements in PD, only the first utility measurement per patient was considered. The number of total observations per health state was N=[REDACTED] in the PFS health state and N=[REDACTED] in the PD health state; therefore, the estimated values are based on few observations (especially for the PD health state) and the analysis does not consider the within-subject correlation.

The descriptive analyses indicate that utilities in the PFS health state appear to be slightly lower at the first measurement than over time, and that the PD health state had a higher mean utility compared with the PFS health state. A slight increase in reported utility values in the PFS health state over time could potentially be explained by a positive treatment effect, such as an improved CR rate and reduced symptom burden compared with other treatment regimens for patients with R/R FL (Table 60). It is also worth noting that the PD utility data are captured at the first follow-up after progression, which may partly explain why mean utility values in the

PD state appear higher than those observed in PFS. This initial PD measurement might reflect a transient period where patients experience an alleviation of symptoms or benefit from supportive care immediately following progression. Additionally, the limited number of observations in the PD state means that these estimates may not fully capture the long-term decline typically associated with disease progression. These factors combined suggest that while the observed trends are somewhat counterintuitive, they can be explained by the timing of utility assessments and the inherent variability in patient-reported outcomes during transitions between health states.

Table 60. Descriptive statistics for utility values based on EPCORE NHL-1 data

Health state	Total observations	Unique subjects	Mean utility (SD)	SE	Median utility	Minimum utility	Maximum utility
PFS (baseline measurement)	■	■	■	■	■	■	■
PFS (all measurements)	■	■	■	■	■	■	■
PD (first measurement) [†]	■	■	■	■	■	■	■
PD (all measurements)	■	■	■	■	■	■	■

[†] As some patients had multiple measurements in PD, the first utility measurement only considered the first PD measurement per patient. The corresponding timepoint differed per patient, as patients progressed at different cycle. PD, progressed disease; PFS, progression-free survival; SD, standard deviation; SE, standard error

UK-specific tariffs were applied to the EQ-5D-3L data in order to obtain UK-specific utilities (Dolan et al. 1997).¹⁰² To estimate utilities from the data, linear mixed models (LMMs) that account for health state (PFS/PD) were fit.

The coefficient estimates and the resulting utility values are displayed in Table 61 and Table 62.

Table 61. Utility model coefficients calculated using EPCORE NHL-1 data

Parameter	Estimate	SE	p-value	95% CI of estimate
Intercept	0.800	0.020	<0.001	(0.760, 0.840)
Health state: PD	0.019	0.0320	0.546	(-0.043, 0.082)

Values are rounded to three decimals for display, but unrounded values were used in the calculation of health state utilities. Abbreviations: CI, confidence interval; SE, standard error; PD, Progressive disease.

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Table 62. Utility values per health state calculated using EPCORE NHL-1 data

Parameters	Health state value
PFS	0.800
PD	0.819

PD, progressed disease; PFS, progression-free survival

The analysis indicates that the utility in the PFS state was 0.800 whereas the utility in the PD state was 0.819. The difference was not statistically significant ($p=0.546$), and the observed increase may be due to random chance and the limited sample size, rather than a true underlying effect.

Recognising that a higher HRQoL in the PD health state compared with the PFS health state lacks face validity, a literature review was conducted to source utility values that could be used to inform modelling of the PD health state, as described in Section 3.4.4. Similarly, given the clinical significance of achieving CR for patients with 4L+ FL, it was also important to explore the potential impact on health state utility of a greater proportion of patients achieving CR with epcoritamab treatment when compared with current 4L+ care in the PF state. Further details are provided in Section 3.4.4.

3.4.2 Mapping

EQ-5D-3L was collected during EPCORE NHL-1; therefore, no mapping algorithms were used between patient-reported outcomes and EQ-5D to derive utilities.

3.4.3 Health-related quality of life studies

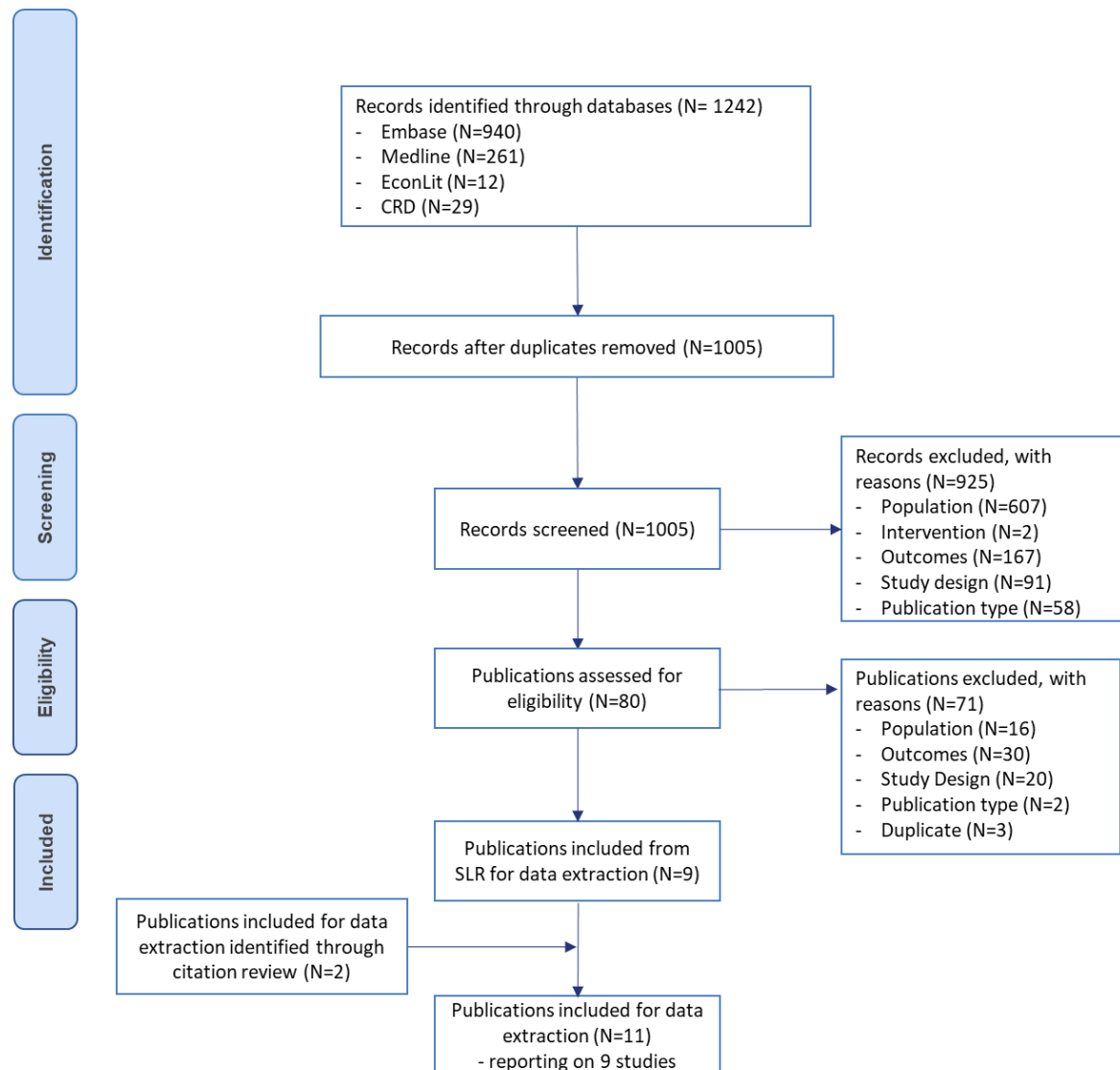
In line with NICE requirements, an SLR was conducted to identify HRQoL studies for the treatment of R/R FL. A full description of SLR methodology and outcomes is provided in Appendix F. A brief overview is provided below.

In brief, electronic database searches (MEDLINE, Embase, EconLit, and Cochrane) searched from inception to 03 April 2023, and subsequently updated on 07 November 2024. Publications describing health state utility values and disutility values for R/R FL were included.

The PRISMA diagram is provided in Figure 35. Eligible studies are described in Appendix F.

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Figure 35. PRISMA diagram illustrating the study selection process for identifying health-related quality of life studies



Nine studies reported HRQoL data in 2L+ patients with R/R FL. Of the nine studies, three¹⁰³⁻¹⁰⁵ included patients with R/R NHL, two of which reported results only for this mixed population (which consisted of >80% FL) and one reported subgroup results for patient with FL. The other six studies¹⁰⁶⁻¹¹¹ included only patients with R/R FL.

Across the studies, the most commonly used instrument to assess HRQoL was EORTC QLQ-C30 (n=5)¹⁰⁷⁻¹¹¹ followed by SF-36 (n=3),¹⁰⁴⁻¹⁰⁶ Functional Assessment of Cancer Treatment-Lymphoma (FACT-Lym) (n=3),^{103,108,109} and EQ-5D (n=3).¹⁰⁷⁻¹¹⁰

Only two studies reported on patients receiving 3L+ therapy.^{108,111}

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Further to the search of electronic databases, a pragmatic review of utility values used in prior NICE TAs was performed (Table 63). As can be seen, EPCORE NHL-1 utility values for the PFS health state closely align with utility values presented in prior HTAs.

Table 63. Overview of utility values used in NICE appraisals in FL

	HTA Appraisal	Source	Utility values
4L+	NICE TA894 ¹¹² Axicabtagene ciloleucel for treating R/R FL	Utilities taken from Wild et al. 2006 ⁸⁵	PFS: 0.805 PD: 0.618
3L+	NICE TA892 ¹¹³ Mosunetuzumab for treating R/R FL	Utilities based on GO29781	PFS: 0.804 PD: 0.75
	NICE TA604 ¹¹⁴ Idelalisib for treating refractory FL	FACT-Lym score cannot be mapped to EQ-5D, so utilities based on Wild et al. 2006 ⁸⁵ . ERG added scenarios with utilities taken from Bec et al. 2014 ¹¹⁵ and GADOLIN trial	Wild et al. 2006: • PFS: 0.81 • PD: 0.62 Bec et al. 2014: • PFS: 0.71 • PD: 0.51 GADOLIN trial: • PFS on treatment: 0.82 • PFS off treatment: 0.81 • PD: 0.76
2L+	NICE TA629 ⁹³ Obinutuzumab with bendamustine for treating FL after rituximab	Utilities based on GADOLIN / TA472	PFS on treatment: 0.822 PFS off treatment: 0.807 PD: 0.758
	NICE TA627 ⁹² Lenalidomide with rituximab for previously treated FL	Utilities for each health state are based on observed EQ-5D-3L data from the AUGMENT trial, with published literature in scenario analysis	PFS: 0.847 PD on treatment: 0.791 PD off treatment: 0.821
	NICE TA137 ⁹¹ Rituximab for the treatment of R/R stage III or IV follicular non-Hodgkin's lymphoma	Utilities taken from Wild et al. 2006 ⁸⁵	PFS: 0.805 PD: 0.618

FL, follicular lymphoma; HTA, health technology assessment; PFS, progression-free survival; PD, progressed disease

3.4.4 Health-related quality-of-life data used in the cost-effectiveness analysis

3.4.4.1 Utilities by complete response status in the PF health state

As detailed previously, engagement with clinical experts indicated that patients who achieve CR are expected to have higher HRQoL than those who do not achieve CR. As outlined in Section 2.8.2, significantly higher rates of CR are achieved on treatment with epcoritamab compared with current 4L+ care. Therefore, to consider the impact of achieving CR on patient HRQoL while they remain progression-free, a utility analysis differentiating PF utilities by 'PF with CR' and 'PF without CR' was performed. This was achieved by dividing patients into each group according to whether they had achieved CR at least once or had never achieved CR at all. The outcomes are presented in Table 64.

Table 64. Utility values in the progression-free health state by CR status

Health state	Total observations	Unique subjects	Mean utility	SE	P-value
PF with CR	195	46	0.832	0.045	0.036
PF without CR	61	35	0.736	0.035	<0.0001

CR, complete response; PF, progression-free; SE, standard error

These utility analyses were implemented into the economic analysis by weighting according to the proportion of patients achieving CR in each of epcoritamab and current 4L+ care as presented in Table 65.

Table 65. Calculation of weighted PF utility incorporating CR status

Therapy	PF with CR		PF without CR		Weighted PF utility
	Mean utility	Proportion achieving CR	Mean utility	Proportion not achieving CR	
Epcoritamab	0.832	■	0.736	■	■
Current 4L+ care		■		■	■

CR, complete response; PF, progression-free

3.4.4.2 Utility in the PD health state

As described in Section 3.4.1, EPCORE NHL-1 did not yield a valid estimate of utility in the PD health state suitable for use in decision making. The values presented by Wild et al. (2006) have been used in various NICE appraisals to represent the

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HRQoL of patients with R/R FL.^{16,18,85,114,116} As such, a utility decrement detailed in Wild et al. (2006) is applied in the base case to calculate the PD utility.⁸⁵

As it was not feasible to differentiate PD utilities by CR status, a single PD utility value was incorporated. To derive this, the utility decrement of -0.187, as reported by Wild et al. (2006),⁸⁵ was applied to the lower PF utility (i.e. that of the current 4L+ care arm), resulting in a PD utility value of [REDACTED]. This value is consistent with the range of PD utilities reported in the published literature. For instance, Wild et al. (2006)⁸⁵ reported a PD utility of 0.618 (also used in TA894), and other sources have even applied lower estimates; Bec et al. (2014)¹¹⁵ reported a PD utility of 0.51.

3.4.4.3 Utility values applied within the base case analysis

The utility values used in the base case analysis are shown in Table 66 and are informed by analysis from EPCORE NHL-1 and Wild et al.,⁸⁵ which was conducted in a population relevant to the UK setting and provided data relevant to the reference case.

Table 66. Utility values applied in the base case

Health state	Utility	Reference
Progression free (epcoritamab)	[REDACTED]	EPCORE NHL-1 4L+ subgroup, HMRN, and Wild et al. (2006) ^{5,117}
Progression free (current 4L+ care)	[REDACTED]	
Progressed disease	[REDACTED]	

3.4.4.4 Age-adjusted utilities

The increasing prevalence of comorbidities in older aged cohorts and the adverse effect on HRQoL directly associated with age must be reflected in economic models with lifetime horizons. It can be assumed that the health state utility values for individuals without a particular health condition will change over the time horizon.

Hence, the economic model includes the use of age-adjusted utility values over the time horizon of the model to account for this. This has been included in the economic model using age- and sex- adjusted utilities from the UK index of health state utility decline in Ara and Brazier.¹¹⁸⁻¹²⁰

3.5 Cost and healthcare resource use identification, measurement and valuation

3.5.1 Resource identification, measurement and valuation studies

Section 3.1 and Appendix G describe how relevant cost and healthcare resource data were identified. Briefly, an SLR was conducted to identify studies describing the costs and resource use associated with the management of patients with R/R FL who had received two or more prior lines of therapy. The literature search identified 16 studies describing costs and resource across 18 different publications.¹²¹⁻¹³⁸ Of the 16 studies, four studies presented evidence among patients receiving therapies in the 3L+ setting.^{123,128,130,131} All the studies that presented evidence among patients receiving 3L+ therapy were retrospective analyses.

Ten studies had a geographical focus in the US, one in Canada, one in Italy, one across multiple locations, and three did not report the geographic focus. All of the studies, except two,^{137,138} reported data on direct healthcare costs and none reported on indirect costs. The most common direct costs reported across the studies included medical costs, inpatient costs, outpatient costs, emergency room (ER) costs, physician office visit costs, pharmacy costs, and FL-specific treatment costs.

All except two^{121,124} studies reported on healthcare resource use. The most common resource use reported across the studies included frequency of inpatient hospitalisations, ER visits, physician office visits, and outpatient visits, length of stay in hospital (inpatient stay, ER visits, ICU admissions), number of days in outpatient services, and number of days with drug administration.

3.5.2 Intervention and comparators' costs and resource use

3.5.2.1 Drug acquisition costs

Drug dosing and administration is aligned with the expected UK label for epcoritamab and the dosing regimens for current 4L+ care in England. Epcoritamab subcutaneous injection was administered according to the dosing regimen described in Table 45. Drug dosing in the economic analysis was converted to the model cycle length of 7 days. Drug unit costs for epcoritamab were sourced from the BNF.¹³⁹ An overview of drug acquisition costs for epcoritamab is presented in Table 67.

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Table 67. Epcoritamab dosing and acquisition costs

Individual drug	Dose per vial	Units per pack	Cost per pack	Price per mg	Reference
Epcoritamab	48mg	1	£6,568.00	£136.83	BNF ¹⁴⁰
	4mg	1	£547.33	£136.83	

BNF, British National Formulary

A relative dose intensity of 100% is applied for the epcoritamab 48 mg dose, while a relative dose intensity of 100% is applied for the 0.16 mg, 0.80 mg, and 3 mg doses.⁹⁰

As detailed in the patient information leaflet for epcoritamab, healthcare professionals may dilute 4 mg vials of epcoritamab to prepare the relevant priming and intermediate doses and minimise wastage; therefore, it is assumed that vial sharing is permitted in the base case analysis.¹⁴¹

Current 4L+ care drug acquisition cost

As described in Section 3.2.3.2, current 4L+ care is modelled through a weighted basket of multiple treatment combinations identified as the most prevalent treatment used for patients with 4L+ R/R FL by HMRN and validated through engagement with UK clinical experts.^{5,9} The current 4L+ care basket is costed using the treatment regimen within each sub-basket that is most used in clinical practice as determined by HMRN and outlined in Table 68. **Error! Reference source not found.**⁵

Table 68. Composition of current 4L+ care regimens applied

Sub-basket	Most prevalent treatment option
R-Chemotherapy	Rituximab + bendamustine
Chemotherapy	Chlorambucil
R ²	Rituximab + lenalidomide
Other immuno-chemotherapy	Obinutuzumab + bendamustine

HMRN, Haematological Malignancy Research Network; R², rituximab with lenalidomide; R-chemotherapy; rituximab with chemotherapy

The dosing regimens for each of these therapies is presented in Table 69.

Table 69. Current 4L+ care dosing regimens

Sub-basket	Therapy		Dose	Administration route	Administration regimen	Reference
R-Chemo	Rituximab + bendamustine	Bendamustine	90 mg/m ²	IV	Cycles 1-6: Day 1 and 2 (28-day cycle)	NHS protocol ¹⁴²
		Rituximab	375 mg/m ²	IV	Cycles 1-6: Day 1 (28-day cycle)	
Chemotherapy	Chlorambucil	Chlorambucil	10 mg	Oral	Cycles 1-6: Day 1-14 (28-day cycle)	South West Clinical Network ¹⁴³
R ²	Rituximab + lenalidomide	Rituximab	375 mg/m ²	IV	Cycle 1: Day 1, 8, 15, 22 (28-day cycle) Cycle 2-5: Day 1 (28-day cycle)	SmPC ¹⁴⁴
		Lenalidomide	20 mg	Oral	Up to 12 cycles: Day 1-21 of 28-day cycles	
Other immuno-therapies	Obinutuzumab + bendamustine	Obinutuzumab	1000 mg	IV	Cycle 1: Day 1, 8, 15 (28-day cycle) Cycles 2-6: Day 1 (28-day cycle) Followed by maintenance every 2 months for 2 years or until disease progression	SmPC ¹⁴⁵
		Bendamustine	90 mg/m ²	IV	Cycles 1-6: Day 1 and 2 (28-day cycle)	South West Clinical Network ¹⁴⁶

IV, intravenous; R², rituximab + lenalidomide; R-Chemo, rituximab with chemotherapy; SmPC, summary of product characteristics

For each individual drug in the basket, the cheapest dose per mg available was selected per eMIT and the BNF, as presented in Table 70.¹³⁹

Table 70. Individual current 4L+ care acquisition costs

Treatment regimen	Individual drug	Dose per tablet/vial	Units per pack	Cost per pack	Source
R-Chemotherapy	Rituximab	100 mg	2	£314.33	BNF ¹⁴⁷
		500 mg	2	£1,571.67	
	Bendamustine	25 mg	5	£40.86	eMIT ¹⁴⁸
		100 mg	1	£91.99	
		100 mg	5	£127.14	
Chemotherapy	Chlorambucil	2 mg	25	£11.00	BNF ¹⁴⁷
R²	Rituximab	100 mg	2	£314.33	BNF ¹⁴⁷
		500 mg	2	£1,571.67	
	Lenalidomide	2.5 mg	21	£26.23	eMIT ¹⁴⁸
		5 mg	21	£31.48	
		7.5 mg	21	£45.16	
		10 mg	21	£27.55	
		15 mg	21	£30.76	
		20 mg	21	£43.27	
		25 mg	21	£28.27	
Other immunotherapies	Obinutuzumab	1000 mg	1	£3,312.00	BNF ¹⁴⁷
	Bendamustine	25 mg	5	£40.86	eMIT ¹⁴⁸
		100 mg	1	£91.99	
		100 mg	5	£127.14	

BNF, British National Formulary; eMIT, drugs and pharmaceutical electronic market information tool; R-Chemo, rituximab + chemotherapy; R², rituximab + lenalidomide

In the base case, the cost of current 4L+ care is modelled through the basket in order to accurately capture the broad range of potential treatments. The dosing frequency per drug is incorporated according to the dosing regimen (Table 69) to calculate the cost per treatment in the basket per cycle. The proportion of patients treated with each therapy, presented in Table 71, is then used to calculate the weighted cost per cycle for the current 4L+ care basket.

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Most regimens within the current 4L+ care basket have a fixed treatment duration; therefore, the accrual of individual drug costs in the basket were calculated in accordance with maximum treatment durations described in their SmPCs. Drug wastage was considered for current 4L+ care regimens by assuming that patients receive only whole vials, and that vial sharing is not permitted in the base case analysis.

Table 71. Proportion and costs of current 4L+ care basket combination treatments

Current 4L+ care basket treatments	Proportion of basket (%)	Source
R-Chemotherapy	████	HMRN ⁵
Chemotherapy	████	
R ²	████	
Other immuno-chemotherapies	████	

[†] Weighted total treatment acquisition and administration costs are presented. In the model, weighted cost per cycle was used to calculate the cost for current 4L+ care basket.

HMRN, Haematological Malignancy Research Network; R², rituximab + lenalidomide; R-Chemotherapy, rituximab + chemotherapy

3.5.2.2 Drug administration costs

Treatments may be administered IV, orally or through subcutaneous injection. Drug administration unit costs were obtained from the National Schedule of Reference Costs by the NHS 2023/2024 and are summarised in Table 72.¹⁴⁹

Epcoritamab monotherapy is expected to be prescribed in either secondary or tertiary care, with routine follow-up also being performed in the same settings. This is consistent with other treatment options currently available for R/R FL.

Clinical experts have noted that current 4L+ care often involves extensive inpatient hospital stays due to the need for regular IV infusions, which can be both time-consuming and taxing on the NHS, patients and carers. Chemotherapy, a large component of this care, can lead to significant side effects and requires continuous monitoring, thereby increasing the burden on healthcare resources and the patient and carer's quality of life. In contrast, epcoritamab monotherapy is administered subcutaneously and is expected to incur a smaller healthcare resource burden.

For drugs administered orally, it was assumed that no hospital resources would be required and thus, costs were assumed to be zero.

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Table 72. Drug administration costs

Administration route	Costs	Reference
IV	£198.08	SB15Z (NHS Reference Costs 2023-24) ¹⁴⁹
Oral	£0	Assumption
SC	£133.39	SB12Z (NHS Reference Costs 2023-24) ¹⁴⁹

IV, intravenous; NHS, National Health Service; SC, subcutaneous

3.5.2.3 Subsequent treatments

Following progression on their 4L treatment (epcoritamab or current 4L+ care) patients could receive subsequent therapy (i.e. $\geq 5^{\text{th}}$ line) in the PD state. Since there is no established standard of care for patients reaching 4L+, the escalation treatment pathway for all primary treatments is expected to be identical for epcoritamab and current 4L+ care because patients are expected to continue recycling old regimens, irrespective of the regimen they received at 4L. Further, it is anticipated that having epcoritamab available as a treatment option in the 4L setting would delay patients' recycling prior treatment regimens by one line of therapy. Therefore, clinical experts have stated that the basket of subsequent treatment should be identical to the basket of current 4L+ care used within the comparator arm, aligned with the approach taken in TA894.^{9,19}

Subsequent therapy costs were calculated based on the dosing schedules for treatments as defined by their SmPC and weighted according to the proportions in Table 71, before being applied as a single cost per cycle for patients receiving subsequent therapy. The cost per cycle is determined by calculating the total cost of each regimen—for drug acquisition and administration costs, respectively, over its full duration and dividing this by the number of cycles within that period. This provides an estimate of the average cost per cycle for each regimen, which is then weighted according to the distribution of subsequent treatments (as per Table 70). This ensures that the cost per cycle appropriately reflects the mix of therapies used in the PD state. The time on treatment and average cost per cycle for each subsequent treatment is displayed in Table 73.

Table 73. Subsequent treatment cost per cycle and time on treatment

Subsequent treatments	Time on treatment (weeks)	Average treatment acquisition cost per cycle	Average administration cost per cycle	Average cost per cycle
R-Chemotherapy	21	████	████	████
Chemotherapy	22	██	██	██
R ²	47	████	████	████
Other immuno-chemotherapies	101	████	████	████

R², rituximab + lenalidomide; R-Chemo, rituximab with chemotherapy

In application, subsequent treatment costs are applied on a per-cycle basis throughout the duration that patients remain in the PD state, rather than as a one-off cost at the point of progression. This approach captures the ongoing resource use associated with subsequent treatments by allocating the costs according to the length of time patients spend in the PD state. Consequently, this method reflects the cumulative impact of subsequent treatments over time ensuring that the costs are aligned with the PD state occupancy.

3.5.2.4 Healthcare resource use

Cost categories describing the management of R/R FL expressed in terms of routine monitoring activities and procedures performed in each health state were informed by resource use estimates from TA892 and validated by clinicians.^{9,16}

Disease management costs were applied to each model cycle where a patient was alive and these costs were different between the PFS and PD health states, independent of treatment arm. They are considered to represent health care resource use that is specific to disease status rather than treatment arm, in line with the approach taken in previous NICE appraisals.^{16,17,19}

Unit costs for resource use activities were sourced from the NHS National Schedule of Reference Costs 2022-23 and previous submissions to NICE.^{150,151}

Table 74. Resource use and monitoring costs applied

Activity	Frequency per cycle			Unit cost	Reference
	PFS	PD	Reference		
Haematologist led consultation	Once a month	Once a month	TA892 and clinical opinion	£204.32	NHS Reference Costs 2023-24 WF01A ^{94,151}
Full blood count	Once a month	Once a month	TA892 and clinical opinion	£7.90	TA892 inflated using PSSRU 2022/2023 ^{94,150,152}
Full profile (U&E, LFT, calcium)	Once a month	Once a month	TA892 and clinical opinion	£21.52	TA892 inflated using PSSRU 2022/2023 ^{94,150,152}
Serum IgG, IgA, IgM and electrophoresis	Once a month	Once a month	TA892 and clinical opinion	£31.58	TA892 inflated using PSSRU 2022/2023 ^{94,150,152}
Lactate Dehydrogenate (LDH) test [†]	Once a month	None	TA892 and clinical opinion	£15.97	TA892 inflated using PSSRU 2022/2023 ^{94,150,152}
Computer tomography (CT) scans [†]	Once a year	None	TA892 and clinical opinion	£142.63	NHS Reference Costs 2023-24 RD27Z ^{94,151}

[†] Based on the ESMO FL guidelines, an LDH test and CT scan are only resourced when patients are still free of progression¹⁵³
CT, computer tomography; Ig, immunoglobulin; LDH, lactate dehydrogenase; LFT, lateral flow test; NHS, National Health Service; PD, progressed disease; PFS, progression-free survival; PSSRU, Personal Social Services Research Unit; U&E, urea and electrolytes

Costs for disease progression and terminal care were included as a one-off cost and are applied when patients first reach the PD health state or the absorbing death health state, respectively. When patients progress, it is assumed all patients (100%) undergo a one-time radiological assessment and a blood test, and 25% undergo a biopsy. These assumptions are in line with TA892.¹⁵⁰ Associated costs for these activities are listed in Table 75.

Table 75. One-off resource use and monitoring costs applied in the analysis

Activity [†]	Disease progression	Unit cost	SE	Reference
Radiological assessment	100%	£102.78	£10.28	NHS Reference Costs 2023-24 RD20A ²⁸
Biopsy	25%	£951.68	£95.17	NHS Reference Costs 2023-24 SA33Z ²⁸
Blood test	100%	£8.04	£0.80	NHS Reference Costs 2023-24 DAPS05 ²⁸

[†] Based on TA892, it is assumed a radiological assessment, biopsy, and blood test are only resourced upon progression or entering terminal care

NHS, National Health Service; SE, standard error

Table 76 presents the terminal care costs sourced for the UK base case. Terminal care costs are applied as a one-off expense at the point when patients enter the death state.

Table 76. One-off costs of terminal care applied in the analysis

Category	Cost	SE	Reference
Terminal care	£7,363.85	£736.38	King's Fund Report; extracted from Mosunetuzumab submission, inflated using PSSRU 2022/2023 ^{150,152}

PSSRU, Personal Social Services Research Unit; SE, standard error

3.5.2.5 Adverse event costs

The total costs of managing adverse events were calculated through summing the multiplication of the AE incidence presented in Section 3.3.3 with the associated costs presented in Table 77. These costs are applied as a one-off expense in the first cycle, ensuring that the management costs for adverse events are incurred only once at the initiation of treatment.

Table 77. Adverse event costs applied within the economic evaluation

Adverse event	Cost	SE	Reference
Anaemia	£5,305.01	£530.50	National Schedule of Reference Costs 2023-24: weighted average of SA03G to SA03H
COVID-19	£2,108.52	£210.85	National Schedule of Reference Costs 2023-24: DX21A
COVID-19 pneumonia	£2,897.93	£289.79	National Schedule of Reference Costs 2023-24: DX11A
Leukopenia/ Leukocytopenia	£560.68	£56.07	National Schedule of Reference Costs 2023-24: Weighted average of SA08G to SA08J
Lymphopenia	£560.68	£56.07	National Schedule of Reference Costs 2023-24: Weighted average of SA08G to SA08J
Neutropenia	£560.68	£56.07	National Schedule of Reference Costs 2023-24: Weighted average of SA08G to SA08J
Neutrophil count decreased	£560.68	£56.07	National Schedule of Reference Costs 2023-24: Weighted average of SA08G to SA08J
Pneumonia	£2,741.34	£274.13	National Schedule of Reference Costs 2023-24: Weighted average of DZ23J:DZ23N

NHS, National Health Service; NICE, National Institute for Health and Care Excellence; SE, standard error

3.6 Severity

The NICE committees consider the severity of a condition when assessing health technologies.¹⁵⁴ The severity of the disease is considered by calculating the absolute QALY shortfall and proportional QALY shortfall by comparing with QALYs in current 4L+ care.

The calculation used to determine absolute QALY shortfall is as follows:

$$\text{Absolute QALY shortfall} = \text{QALYs in current 4L+ care} - \text{QALYs in age and sex matched general population}$$

The calculation used to determine proportional QALY shortfall is as follows:

$$\text{Proportional QALY shortfall} = \frac{\text{Absolute QALY shortfall}}{\text{QALYs in age and sex matched general population}}$$

In the base case analysis, with a mean age at baseline of 64.8 years and a proportion of males of 65.4%, the absolute shortfall estimate is 9.92 QALYs and the proportional shortfall is 90.93%, which results in a severity modifier of ×1.2 (Table Company evidence submission for epcoritamab for treating relapsed or refractory follicular lymphoma patients after three or more systemic treatments)

78). This is calculated using the reference case in the York QALY shortfall calculator (using English life tables, the EQ-5D-3L value set and scoring algorithm, and adjusted limited dependent variable mixture models).^{118,155-157} This $\times 1.2$ severity modifier is applied to the incremental QALYs in the model base case. The application of a severity modifier in 4L+ FL aligns with clinician and patient feedback where the life expectancy with current 4L+ care in England is low (median OS reached by ■ months) and patients will typically be re-challenged with a variant of CIT or chemotherapy.

Table 78. QALY shortfall calculation results

Outcome	Total QALYs	Shortfall	
		Absolute	Proportional
General Population	10.91		
R/R FL-Specific	0.9851	9.92	90.93%
QALY Multiplier	-	$\times 1$	$\times 1.2$

Values are based on discounted QALYs

FL, follicular lymphoma; QALY, quality adjusted life year; R/R, relapsed/refractory

The conclusion of a $\times 1.2$ severity modifier is durable to variations in the choice of scoring algorithm and health state profile, increasing confidence that a $\times 1.2$ modifier is appropriate and suitably reflects the severity of patients with 4L+ R/R FL.

3.7 Uncertainty

Due to the limited literature reporting data on patients with 4L+ R/R FL, this analysis is subject to inescapable uncertainty; therefore, the available data may not fully capture the variability and complexity of patient responses and outcomes in 4L+ FL. Although efforts have been made to engage with clinicians experienced in treating patients with 4L+ R/R FL to validate model inputs and patient outcomes, the absence of robust published estimates for resource use and burden of current therapies on patients and caregivers means that this analysis may underestimate the value of epcoritamab compared with existing current 4L+ care options. The benefits of epcoritamab which could not be robustly captured within the economic analysis are detailed in Section 3.13, and include a reduced HRQoL burden relative to treatment with chemoimmunotherapy regimens, less frequent HCRU through more patients achieving CR (where resource utilisation is less intense), anticipated reduction in

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cardiac adverse events compared with treatment using CIT regimens, and alleviated caregiver burden/anxiety.

Further, although unavoidable due to ethical considerations around treating patients at 4L+, EPCORE NHL-1 is a single arm clinical trial; therefore, no data directly comparing its efficacy with current 4L+ care options are available. This increases the uncertainty within the presented analyses by limiting the ability to establish a direct relationship between treatment effect and observed outcomes and increases the potential for biases in the interpretation of the results. To increase committee confidence in the outputs of the trial and cost-effectiveness analyses, clinical consultations were held to validate the design and outcomes of EPCORE NHL-1, as outlined in Section 3.14.1. Further, to obtain a robust comparison of epcoritamab efficacy compared with current 4L+ care, a MAIC was performed leveraging precedent and recommendations from previous NICE appraisals for similar patient populations and recommendations from clinicians, as detailed in Section 2.12.

Moreover, the lack of recent positive recommendations from NICE, and the poor outcomes observed in HMRN for treatments in 4L+ FL further highlights the significant unmet need in this patient population. The absence of established guidelines and positive recommendations underscores the urgency for innovative and effective treatments, providing a compelling rationale for the continued exploration and development of new therapeutic options.

The company has made conscientious efforts to limit the uncertainties within this appraisal. Since epcoritamab represents a promising advancement in the treatment of patients with 4L+ R/R FL, remaining uncertainties should not act as a barrier to ensuring an efficacious treatment is made available to patients, in an area of high unmet need.

3.8 Managed access proposal

Data available at the time of submission and presented within this dossier are sourced from the [REDACTED] data cut-off for EPCORE NHL-1 and indirectly compared with treatment options offered in NHS practice. These data provide sufficient evidence for the clinical and cost-effectiveness of epcoritamab as a

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treatment for R/R FL in patients who have previously received three lines of prior therapy, demonstrating that it represents a cost-effective use of NHS resources and may be recommended for routine use. A managed access agreement may be considered if there is any need to address residual uncertainty.

3.9 Summary of base-case analysis inputs and assumptions

3.9.1 Summary of base case analysis inputs

A summary of all values used in the base case analysis is presented in Table 79.

Table 79. Summary of variables applied in the base case analysis

Variable	Value	Measurement of uncertainty and distribution	Section
Baseline parameters			
Baseline parameters	Table 43	% Female: Beta Others: Normal	3.2.1
Survival functions			
PFS extrapolation	Log-normal	Distribution-specific	3.3.2.4
OS extrapolation	Log-normal	Distribution-specific	3.3.2.3
TTD extrapolation: Epcoritamab	Log-normal	Distribution-specific	3.3.2.5
TTD extrapolation: Current 4L+ Care	Exponential	Distribution-specific	3.3.2.5
Clinical parameters			
Adverse events rates	Table 58	Beta	3.3.3
Utilities	Table 66	Beta	3.4.4
Costs			
Epcoritamab dosing and acquisition costs*	Table 67	None	3.5.2.1
Current 4L+ care dosing and acquisition costs	Table 70	None	3.5.2.1
Current 4L+ care proportions	Table 71	Dirichlet	3.5.2.1
Drug administration costs	Table 72	Gamma	3.5.2.2
Subsequent treatment costs	Table 73	Gamma	3.5.2.3
Healthcare resource use	Table 74 Table 75	Gamma	3.5.2.4

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	Table 76		
AE costs	Table 77	Gamma	3.5.2.5

*Model results have been run using the current epcoritamab PAS price.

AE, adverse event; OS, overall survival; PFS, progression-free survival; TTD, time to treatment discontinuation

3.9.2 Summary of assumptions

A summary of assumptions made in the base case analysis is presented in Table 80.

Table 80. List of key assumptions

Category	Assumption in base case	Justification	Addressed in scenario analysis
Survival models			
PFS curves	Base case: Log-normal	IPD from EPCORE NHL-1 were used to extrapolate long-term PFS outcomes. EPCORE NHL-1 provides direct clinical evidence for the efficacy of epcoritamab in the population of interest in this submission. The selection of extrapolation for PFS was based on statistical fit, visual inspection and long-term clinical plausibility, as validated by UK clinical experts	Scenario analyses have been conducted in which alternative appropriate extrapolations were selected to model PFS for epcoritamab
OS curves	Base case: Log-normal	IPD from EPCORE NHL-1 were used to extrapolate long-term OS outcomes. EPCORE NHL-1 provides direct clinical evidence for the efficacy of epcoritamab in the population of interest in this submission. The selection of extrapolation for OS was based on statistical fit, visual inspection and long-term clinical plausibility, as validated by UK clinical experts	Scenario analyses have been conducted in which alternative extrapolations were selected to model OS for epcoritamab
TTD curve: epcoritamab	Base case: Log-normal	IPD from EPCORE NHL-1 were used to extrapolate long-term TTD outcomes. EPCORE NHL-1 provides direct clinical evidence for the efficacy and tolerability of epcoritamab in the population of interest in this submission. The selection of extrapolation for TTD was based on statistical fit, visual	Scenario analyses have been conducted in which alternative extrapolations were selected to model TTD for epcoritamab

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		inspection and long-term clinical plausibility, as validated by UK clinical experts	
TTD curve: current 4L+ care	Raw HMRN TTD data is extrapolated for modelling discontinuation from current 4L+ care Base case: Exponential	Direct use of the HMRN TTD data was preferred, given it would not be appropriate to derive a hazard ratio for TTD between epcoritamab and current 4L+ care given the differences in dosing schedules and treatment durations between regimens	A scenario analysis is explored where a hazard ratio (HR) derived from comparing raw HMRN PFS and TTD data can be applied to the MAIC-adjusted HMRN PFS curve
Indirect treatment comparison			
Comparative efficacy estimates	Comparative efficacy estimates are based on the outcomes from the FL1-3A cohort from EPCORE NHL-1 who had reached 4L+, modified to censor COVID-19-related deaths, and matched to HMRN via an unanchored MAIC.	This approach was chosen to limit heterogeneity between the epcoritamab population and the comparator data, and addresses the risk of confounding by extrapolating data from EPCORE NHL-1 and comparing them with HMRN. This methodology aimed to ensure that the estimates are as reflective as possible of the target population and UK clinical practice.	No scenario analyses have been conducted varying this approach.
Costs			
Drug acquisition costs	Certain current 4L+ care regimens are assumed to be representative for alternative therapies (e.g. R-Benda represents R-based chemotherapy; Chlorambucil represents chemotherapy; Obinutuzumab + Bendamustine represents other immune-chemotherapies in HMRN).	This assumption simplifies cost calculations by using surrogate regimens that have been validated through clinical expert input and are aligned with previous NICE submissions.	A scenario analysis explores the use of proportions matching the composition of current care in 4L+ basket in TA894.
Drug administration costs	Administration costs are based on NHS Reference Costs (2023-24) and are applied per administration	These costs reflect routine practice in the NHS and are consistent with previous appraisals. The approach	No scenario analyses have been conducted varying this assumption.

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	according to the mode of administration (IV, SC, or oral).	ensures that administration resource use is accurately captured for each treatment modality.	
Healthcare resource use	Healthcare resource use estimates are based on the inputs used in TA892 and were validated through engagement with UK clinical experts.	Input from clinical experts stated that these values are most likely to reflect the resource use of patients with 4L+ R/R FL in UK clinical practice.	Scenario analysis has been performed to measure the impact of applying resource use estimates from TA894.
Utility values			
Utility values	Utility values are sourced from EPCORE NHL-1 using a linear mixed model and are applied as follows: • PF utility: 0.800 (weighted by CR status) ◦ Epcor PF: [REDACTED] ◦ Current 4L+ care PF: [REDACTED] • PD utility: Derived by applying a decrement (– 0.187) to the lower PF utility (current 4L+ care), resulting in [REDACTED].	EPCORE NHL-1 provided patient-reported EQ-5D-3L data, which were used to derive health state utilities. The approach is consistent with NICE reference case methods and validated by clinical experts. Clinical feedback to the company suggested it is important to capture the clinically significant impact on HRQoL of achieving CR and as such PF utility values have been weighted according to exploratory analyses used to derive PF utility values for those who achieved/did not achieve CR and the proportion of patients achieving CR in each arm. For the PD state, the decrement applied is based on Wild et al. (2006) and aligns with values used in previous NICE appraisals, despite the counterintuitive result of higher utility in PD in the trial data.	Scenario analyses have been conducted using alternative utility values identified from the published literature as outlined in Section 3.11.3.3.
Age-related disutility	Utility values in the cost-effectiveness model were age-adjusted based on published decrements from the study by Ara and Brazier	This approach accounts for the natural decline in HRQoL with aging and is consistent with NICE DSU TSD 12 recommendations.	No scenario analyses have been conducted varying this assumption.

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Subsequent treatments			
Subsequent treatments	The proportion of patients receiving subsequent treatments and the distribution of subsequent treatments received were informed by the HMRN registry and validated by UK clinical experts.	EPCORE NHL-1 data on subsequent treatments were deemed less applicable to UK clinical practice. Clinician estimates using data from HMRN provide a more accurate representation of treatment patterns in the NHS.	Scenario analyses exploring the use of proportions matching the composition of current care in 4L+ basket in TA894 also update the proportions of subsequent treatments to reflect clinical experts' feedback that the basket of subsequent treatment should be identical to the basket of current 4L+ care used within the comparator arm
Adverse Events (AEs)			
AE proportions	TEAEs of grade 3 or above that occurred in ≥5% of the patients in EPCORE NHL-1 or data sources reporting current 4L+ care were included in the cost-effectiveness model.	This approach is consistent with common practice in oncology economic models and previous NICE submissions, ensuring that only clinically significant events that impact costs are captured.	No scenario analyses have been conducted varying this assumption.

AEs, adverse events; CR, complete response; DSU, Decision Support Unit; FL, follicular lymphoma; HMRN, haematological malignancy research network; HRQoL, health-related quality of life; IPD, individual patient data; MAIC, match adjusted indirect comparison; OS, overall survival; PD, progressive disease; PFS, progression free survival; QALY, quality adjusted life year; R/R, relapsed/refractory; SC, subcutaneous; TEAE, treatment emergent adverse events; TSD, technical support document; TTD, time to disease

3.10 Base-case results

The base case incremental cost-effectiveness results for epcoritamab (PAS price) compared with current 4L+ treatment options are presented in Table 81. As can be observed, epcoritamab is considered to be a cost-effective use of NHS resources compared with current treatment options in patients with 4L+ R/R FL.

The model predicts mean undiscounted LYs of 1.74 for current 4L+ care, correlating to discounted QALYs of 1.18 (with a x1.2 severity modifier applied). It was predicted that treatment with epcoritamab will result in an additional 3.99 discounted QALYs versus current 4L+ when a severity modifier of ×1.2 is applied.

Total discounted costs associated with epcoritamab (with PAS), accrued over the modelled time horizon, were predicted to be £[REDACTED], which was higher than current 4L+ care (incremental: £[REDACTED]). When a severity modifier of ×1.2 is applied, the resulting ICER estimate for epcoritamab is £[REDACTED] per QALY gained versus current 4L+ care, and when no severity modifier is applied, the resulting ICER is £[REDACTED]/QALY. Therefore, the base case ICER is comfortably below the £30,000 per QALY threshold, demonstrating that epcoritamab can be considered a cost-effective use of NHS resources.

Table 81. Base-case results

	Total			Incremental			
Technologies	Costs (£)	LYs	QALYs	Costs (£)	LYs	QALYs	ICER (£/QALY)
Epcoritamab	[REDACTED]	8.758	5.176	-	-	-	-
Current 4L+ Care	[REDACTED]	1.740	1.182	[REDACTED]	7.018	3.994	[REDACTED]

Analysis performed using epcoritamab PAS price
Costs and QALYs discounted; LYs undiscounted
Severity modifier of ×1.2 applied
ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years

A summary of net monetary benefit (NMB) and net health benefit (NHB) outcomes in the base case is provided in Table 82.

Table 82. Net benefit results in the base case analysis

Net monetary benefit (NMB) at £30,000	Net health benefit (NHB) at £30,000

Analysis performed using epcoritamab PAS price
Severity modifier of $\times 1.2$ applied
NHB, net health benefit; NMB, net monetary benefit

3.11 Exploring uncertainty

3.11.1 Probabilistic sensitivity analysis

The probabilistic sensitivity analysis (PSA) assesses model uncertainty by varying model parameters simultaneously over 1,000 iterations to estimate the range of possible outcomes. NICE guidelines state the number of iterations should be chosen such that stochastic results converge towards an equilibrium.⁸⁴

The distribution chosen for each parameter included in the probabilistic sensitivity analysis PSA (and DSA) is based on the recommendations provided in Briggs et al. (2006).¹⁵⁸ Correlated parameters (such as shares) are modelled through a Dirichlet distribution where applicable.

Where available, the parameters for the distributions in the PSA were derived from the deterministic value and the SE from these deterministic input estimates. In absence of estimates of variance, an SE level of 10% was assumed in line with prior NICE submissions.¹⁵⁹

The findings are presented by means of the cost-effectiveness acceptability curve (CEAC), cost-effectiveness acceptability frontier (CEAF), and a scatter plot of the incremental cost versus the incremental QALYs. Mean total costs, mean total QALYs, and the mean probabilistic ICER are presented for/versus each comparator.

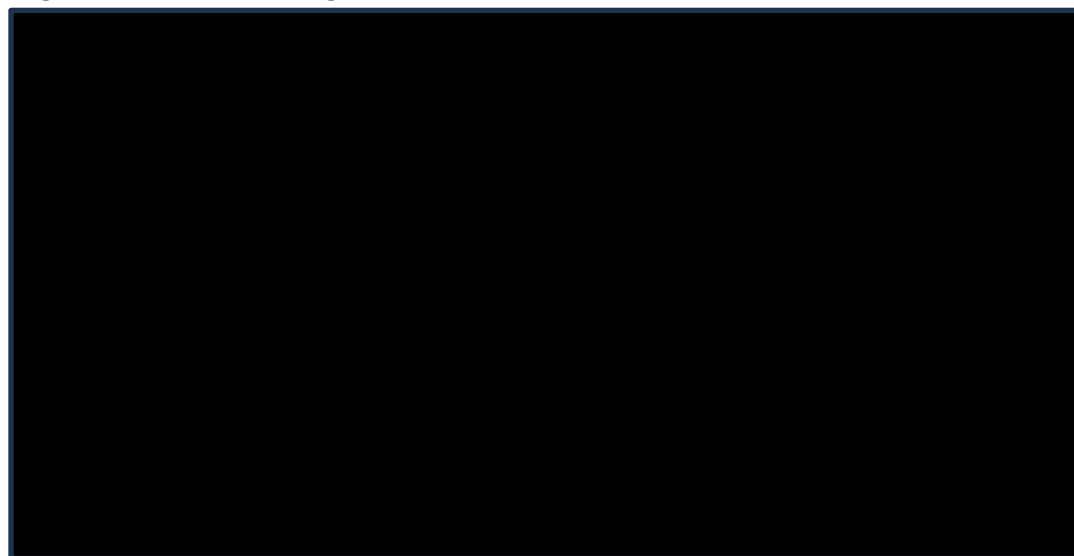
3.11.1.1 Probabilistic sensitivity analysis results

In the PSA, the model samples values from distributions around the means of input parameters using both the mean and SE of parameters to derive an estimated value using an appropriate distribution.

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As can be seen in Figure 36, convergence was reached after roughly 110 simulations; therefore, the estimate of the probabilistic ICER can be considered relatively stable. Further, running 1000 simulations provides a distribution of incremental results, and consequently a robust estimate of the overall uncertainty surrounding the cost-effectiveness of epcoritamab compared with current 4L+ care.

Figure 36. PSA convergence plot



Analysis performed at epcoritamab PAS price

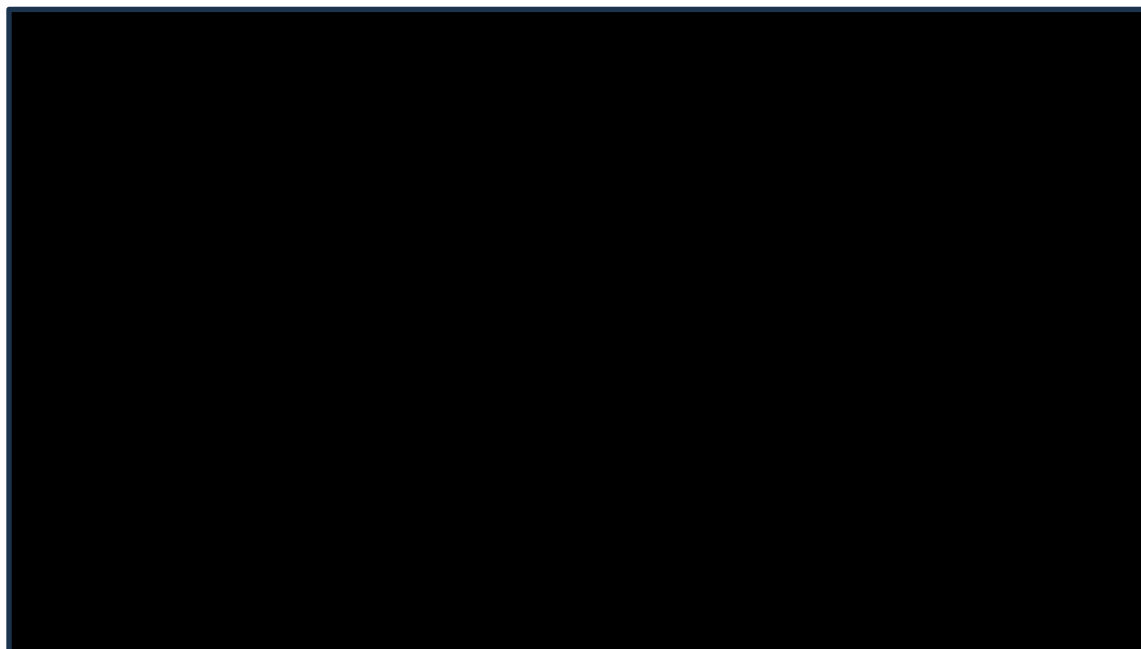
No severity modifier applied

ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year

As the PSA samples each parameter individually according to their mean and standard error, the output of this analysis cannot robustly incorporate a severity modifier as variations in individual parameters may impact absolute and proportional QALY shortfall. In the context of this sensitivity analysis, the severity modifier should instead be considered to apply to the WTP threshold (i.e. a severity modifier of $\times 1.2$ results in a WTP threshold of £36,000/QALY).

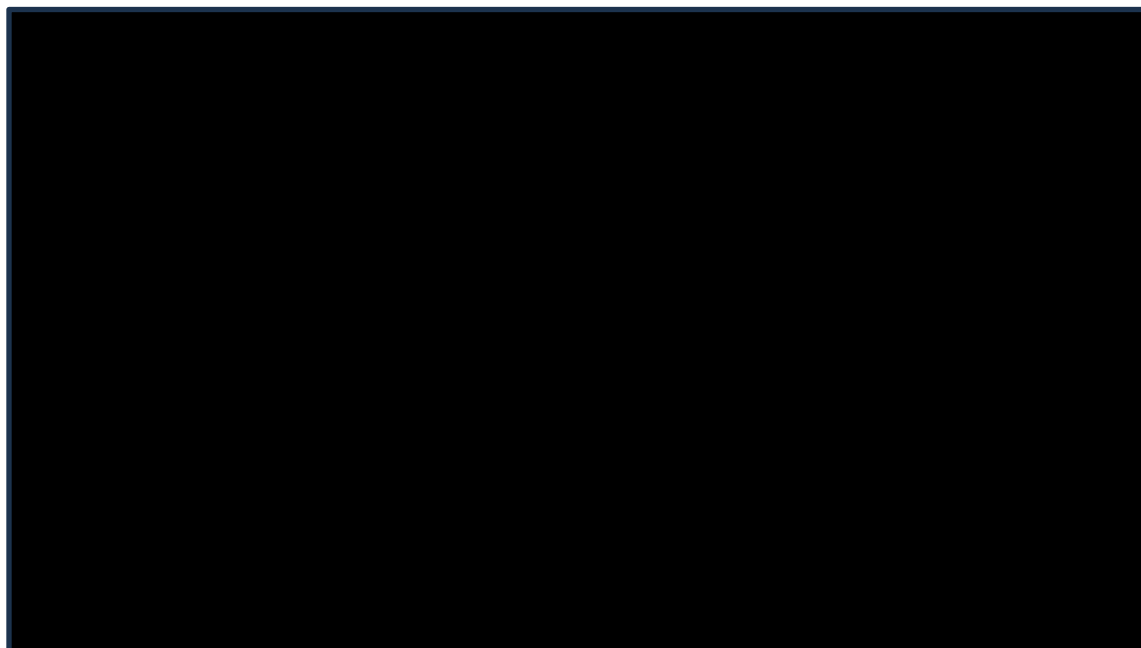
The cost-effectiveness scatter plot and cost-effectiveness acceptability curves for epcoritamab compared with current 4L+ care, arising from 1,000 simulations of the model with all parameters sampled, are presented in Figure 37 and Figure 38.

Figure 37. Cost-effectiveness scatter plot for epcoritamab versus current 4L+ care



Analysis performed at epcoritamab PAS price
No severity modifier applied
QALY, quality-adjusted life years

Figure 38. Cost-effectiveness acceptability curve for epcoritamab versus current 4L+ care



Analysis performed at epcoritamab PAS price
No severity modifier applied
QALY, quality-adjusted life years

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The results of the probabilistic sensitivity using the base case settings are presented in Table 83.

Table 83. Probabilistic base-case results

Technologies	Total		Incremental		
	Costs (£)	QALYs	Costs (£)	QALYs	ICER (£/QALY)
Epcoritamab	■	4.404	-	-	-
Current 4L+ Care	■	1.066	■	3.338	■

Analysis performed using epcoritamab PAS price
Costs and QALYs discounted; LYs undiscounted
No severity modifier applied, as outlined in text above
ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years

Based on these analyses, the probability that epcoritamab is cost-effective versus current 4L+ care is ■% at a willingness to pay (WTP) threshold of £36,000/QALY gained, strengthening the conclusion that epcoritamab provides a cost-effective use of NHS resources compared with current 4L+ care.

3.11.2 Deterministic sensitivity analysis

The deterministic sensitivity analysis (DSA) is a form of one-way sensitivity analysis that adjusts each parameter one at a time to assess the impact of uncertainty around individual input parameters on the incremental costs, incremental QALYs and ICER. Where available, lower and upper bounds for the DSA were determined by the SE from input estimates. In absence of estimates of variance, an SE level of 10% was assumed. An overview of the parameters varied within the DSA is presented in Appendix L.

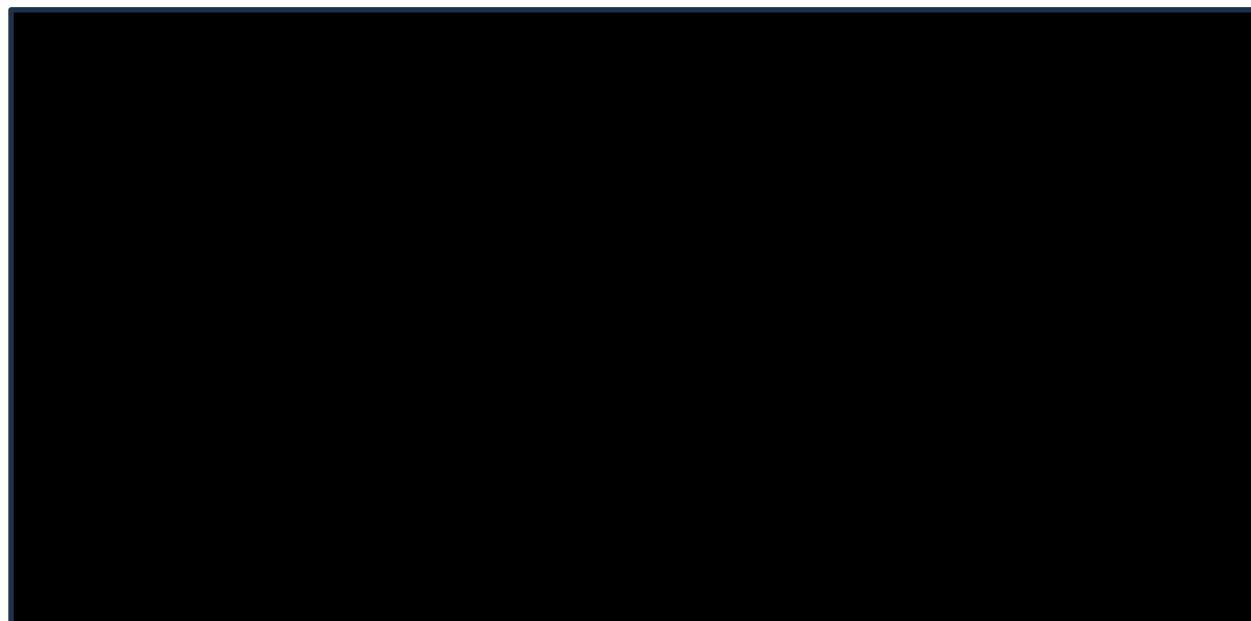
3.11.2.1 Deterministic sensitivity analysis results

Results of the DSA are presented in Figure 39 and demonstrate the impact of specific parameters on ICER estimates.

The DSA samples each parameter individually according to their assigned upper and lower bounds; therefore, similar to the PSA, this sensitivity analysis cannot incorporate the severity modifier applied in the base case analysis as variations in individual parameters may impact absolute and proportional QALY shortfall, thereby impacting whether the threshold for implementing a severity modifier is reached. As previously Company evidence submission for epcoritamab for treating relapsed or refractory follicular lymphoma patients after three or more systemic treatments

stated, the severity modifier should instead be considered to apply to the WTP threshold (i.e. a severity modifier of $\times 1.2$ results in a WTP threshold of £36,000/QALY).

Figure 39. DSA tornado plot for epcoritamab versus current 4L+ care



Analysis performed using epcoritamab PAS price
No severity modifier applied, as outlined in text

The parameter with the greatest impact on the ICER is the HR for OS between epcoritamab and current 4L+ care, acting as the key uncertainty for both the incremental costs and incremental QALYs. The PF utility value calculated using the proportion of patients achieving CR in EPCORE NHL-1 and HMRN also had a large impact on the ICER, primarily through adjustments to incremental QALYs. The remaining parameters had a minimal impact on ICER estimates. None of the sensitivity analyses resulted in the ICER for epcoritamab compared with current 4L+ care exceeding the WTP threshold (with the severity modifier considered).

To assess the impact of these uncertainties on the analysis, plausible scenarios relating to extrapolation of survival data and utility analyses have been performed in Section 3.11.3.

3.11.3 Scenario analysis

3.11.3.1 Time horizon

A scenario analysis was performed to assess the impact of shorter patient survival on model outcomes. Scenarios exploring costs and QALYs at 10 and 20 years were performed as presented in Table 84.

Table 84. Scenario analysis: Model time horizon

		Total			Incremental			
		Costs	LYs	QALYs	Costs	LYs	QALYs	ICER (£/QALY)
10 years	Epcoritamab	██████	5.651	3.965	-	-	-	-
	Current 4L+ Care	██████	1.696	1.165	██████	3.955	2.800	██████
20 years	Epcoritamab	██████	8.009	4.956	-	-	-	-
	Current 4L+ Care	██████	1.739	1.182	██████	6.270	3.774	██████

Analysis performed using epcoritamab PAS price
Costs and QALYs discounted; LYs undiscounted
Severity modifier of ×1.2 applied
ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years

The scenario analysis evaluating the impact of a shorter time horizon on model outcomes demonstrates that reducing the time horizon leads to a decrease in both total QALYs and incremental QALYs gained with epcoritamab compared to current 4L+ care. At a 10-year horizon, incremental QALYs decrease to 2.800 (compared with 3.994 in the base case), resulting in a higher ICER of ██████/QALY. A time horizon of 20 years also reduces the incremental QALYs to 3.774, with an ICER of ██████/QALY, although this is closer to the base-case ICER of ██████/QALY. These results indicate that while a shorter time horizon reduces the estimated benefits of epcoritamab, it remains cost-effective across all scenarios, with ICERs remaining below the £30,000/QALY willingness-to-pay threshold. This underscores the robustness of the cost-effectiveness conclusion despite uncertainty in long-term survival projections.

3.11.3.2 Maximal treatment duration for complete responders

As outlined in Section 3.3.2.5, a maximal treatment duration of three years is applied for complete responders in the base case analysis based on clinical estimates and Company evidence submission for epcoritamab for treating relapsed or refractory follicular lymphoma patients after three or more systemic treatments

durability of response after achieving CR. The impact of shortening this duration to two years to align with clinical opinion from some experts is explored as a scenario, and the outcomes are presented in Table 85.

Table 85. Scenario analysis: Maximal treatment duration for complete responders

		Total			Incremental			
		Costs	LYs	QALYs	Costs	LYs	QALYs	ICER (£/QALY)
2 years	Epcoritamab	████	8.758	5.176	-	-	-	-
	Current 4L+ Care	████	1.740	1.182	████	7.018	3.994	████

Analysis performed using epcoritamab PAS price

Costs and QALYs discounted; LYs undiscounted

Severity modifier of ×1.2 applied

ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years

Consistent with the shorter time on treatment for patients receiving epcoritamab in this two-year maximal treatment duration scenario, lower drug-related costs are incurred in this analysis resulting in a corresponding decrease in the ICER compared with the base case.

3.11.3.3 Source of utility values

The model base case uses the PF utilities split by CR rates derived from EPCORE NHL-1 and HMRN, and a PD utility calculated by applying the utility decrement for disease progression published in Wild et al.⁸⁵ Scenario analyses have been conducted to assess alternative health state utility values, as outlined in Table 86.

Table 86. Utility values applied in scenario analysis

Scenario	Treatment	PF	PD
Utilities for PF from EPCORE NHL-1 trial (adjusted for PD using Wild et al. 2006 ⁸⁵)	Overall	0.800	0.613
Utilities for PF from EPCORE NHL-1 trial (adjusted PD from TA892)	Overall	0.800	0.746
Wild et al. 2006 ⁸⁵	Overall	0.805	0.618
Cognet et al. 2015 ¹⁶⁰	Overall	0.710	0.510
TA892 ¹⁶	Overall	0.804	0.750

PD, progressed disease; PF, progression-free

Table 87 provides an overview of outcomes.

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Table 87. Scenario analysis: Source of utility values

		Total			Incremental			
		Costs	LYs	QALYs	Costs	LYs	QALYs	ICER (£/QALY)
EPCORE NHL-1 with Wild et al. PD adjustment ⁸⁵	Epcoritamab	██████	8.758	5.414	-	-	-	-
	Current 4L+ Care	██████	1.740	1.287	██████	7.018	4.127	██████
EPCORE NHL-1 with TA892 PD adjustment ¹⁶⁰	Epcoritamab	██████	8.758	5.892	-	-	-	-
	Current 4L+ Care	██████	1.740	1.437	██████	7.018	4.456	██████
Wild et al. ⁸⁵	Epcoritamab	██████	8.758	5.452	-	-	-	-
	Current 4L+ Care	██████	1.740	1.296	██████	7.018	4.155	██████
Cognet et al. ¹⁶⁰	Epcoritamab	██████	8.758	4.675	-	-	-	-
	Current 4L+ Care	██████	1.740	1.098	██████	7.018	3.578	██████
TA892 ¹⁶	Epcoritamab	██████	8.758	5.916	-	-	-	-
	Current 4L+ Care	██████	1.740	1.438	██████	7.018	4.478	██████

Analysis performed using epcoritamab PAS price

Costs and QALYs discounted; LYs undiscounted

Severity modifier of ×1.2 applied

ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years

The scenario analysis assessing alternative health state utility values demonstrates that while variations in utility inputs influence QALYs and ICERs, epcoritamab remains cost-effective in all cases. Compared with the base case, the highest QALYs are observed when applying TA892 utility values, resulting in an incremental QALY gain of 4.478 and the lowest ICER of £██████/QALY. The lowest QALYs are seen with Cognet et al.¹⁶⁰ values, where incremental QALYs decrease to 3.578, leading to the highest ICER of £██████/QALY. Other sources, including Wild et al.⁸⁵ and EPCORE NHL-1 with alternative PD adjustments, produce ICERs ranging between ██████ and ██████/QALY. The base-case utility value yielded an ICER of ██████/QALY, which sits between the highest and lowest values observed, indicating that it does not overestimate or underestimate cost-effectiveness. This suggests that the base-case utility choice is a reasonable and balanced assumption, reinforcing the robustness of the cost-

effectiveness results. Despite differences in utility assumptions, epcoritamab consistently remains below the £30,000/QALY willingness-to-pay threshold.

3.11.3.4 Composition of current 4L+ care treatment basket

As outlined in Section 1.3.6.2.3 and Section 3.2.3.2, there is no standard of care for patients with R/R FL, particularly at later lines of therapy where patients mostly recycle through prior treatment regimens to which they may be refractory. In the base case analysis, the composition of the current 4L+ care treatment basket is based on data obtained from HMRN to best reflect UK clinical practice. To recognise the variation in treatment regimens available for patients with 4L+ R/R FL, a scenario has been performed to explore possible variations in prescribing patterns in clinical practice (Table 88). The proportion of treatment received in current 4L+ care is also applied to subsequent rounds of treatment to reflect clinical experts’ feedback that the basket of subsequent treatment should be identical to the basket of current 4L+ care used within the comparator arm, aligned with the approach taken in TA894.^{9,19}

Table 88. Current 4L+ care basket proportions applied in scenario analysis (Taken from TA894)

Scenario	Current 4L+ care basket treatments	Proportion of basket (%)
TA894	R-Chemotherapy	64.2%
	Chemotherapy	0%
	R ²	22.5%
	Other immuno-chemotherapies	13.3%

R², rituximab + lenalidomide; R-Chemotherapy, rituximab with chemotherapy

In this scenario, the increased use of regimens such as R² and other immuno-chemotherapies which incur higher treatment costs, coupled with a reduced reliance on inexpensive options such as chemotherapy, leads to increased drug acquisition costs for the current 4L+ care arm.

As illustrated in Table 89, the higher treatment acquisition costs in the comparator arm in this scenario, compared with the base case analysis, result in a more favourable ICER of £[REDACTED]/QALY. These results indicate that the composition of the 4L+ care

basket has some impact on absolute costs, but does not alter the QALYs gained or the overall conclusion of cost-effectiveness for epcoritamab.

Table 89. Scenario analysis: Composition of current 4L+ care treatment basket

		Total			Incremental			
		Costs	LYs	QALYs	Costs	LYs	QALYs	ICER (£/QALY)
TA894	Epcoritamab	██████	8.758	5.176	-	-	-	-
	Current 4L+ Care	██████	1.740	1.182	██████	7.018	3.994	██████

Analysis performed using epcoritamab PAS price
Costs and QALYs discounted; LYs undiscounted
Severity modifier of ×1.2 applied
ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years

Importantly, this scenario underscores that the cost-effectiveness outcomes for epcoritamab remain robust to variations in the treatment proportions within the current 4L+ care basket, with the ICER staying well below the £30,000/QALY willingness-to-pay threshold. The base-case assumption remains most appropriate as it captures treatment compositions most aligned with clinical practice, as validated by UK clinical experts.

3.11.3.5 Survival extrapolations

Survival modelling using long-term extrapolation of parametric functions is subject to considerable uncertainty despite efforts to robustly and transparently provide survival curves that best represent patients in clinical practice. In order to assess the impact of alternative parametric extrapolations on the cost-effectiveness of epcoritamab, scenario analyses were performed by applying distributions generating clinically plausible outcomes.

This analysis should be viewed within the context of identifying the most appropriate survival extrapolation, as detailed in Section 3.3.2.2. Only extrapolations considered clinically plausible based on engagement with clinicians (Table 49, Table 52 and Table 55) have been included.

3.11.3.5.1 Epcoritamab OS

To understand the impact of varying which distribution is used to extrapolate OS outcomes for epcoritamab, a scenario analysis was performed varying the selected OS distribution while preserving the base case settings for PFS and TTD.

As shown in Table 90, epcoritamab remains cost-effective under all plausible extrapolations, reinforcing the robustness of the cost-effectiveness conclusion under varying survival assumptions. Despite these variations, the base-case log-normal extrapolation provides a balanced estimate, with an ICER of █████/QALY reinforcing its suitability as a reasonable assumption in the absence of long-term survival data. While OS extrapolation remains a source of uncertainty, epcoritamab maintains cost-effectiveness across all clinically plausible scenarios.

Table 90. Scenario analysis: Epcoritamab OS

Epcoritamab OS extrapolation	Total			Incremental (compared with current 4L+ care)			
	Costs	LYs	QALYs	Costs	LYs	QALYs	ICER (£/QALY)
Log-normal	████	8.758	5.176	████	7.018	3.994	████
Log-logistic	████	8.041	4.909	████	6.369	3.757	████
Gompertz	████	7.732	4.780	████	6.092	3.643	████

Costs and QALYs discounted; LYs undiscounted
Severity modifier of ×1.2 applied
Base case extrapolation marked in blue text
ICER, incremental cost-effectiveness ratio; LYs, life years; OS, overall survival; QALYs, quality-adjusted life years

3.11.3.5.2 Epcoritamab PFS

Similar to the previous scenario, to understand the impact of varying which distribution is used to extrapolate PFS outcomes for epcoritamab, a scenario analysis was performed varying the selected PFS distribution while preserving the base case settings for OS and TTD. In addition to exploring the impact of clinically plausible distributions according to clinicians estimates, a scenario was explored using the generalised gamma distribution for epcoritamab PFS; the generalised gamma distribution provided the best fit to the observed data and also matched clinicians estimates up to 5 years, with only a slight overestimation of outcomes at 10 years.

As shown in Table 91, despite variations, the base-case log-normal distribution provides a reasonable balance, ensuring a cost-effectiveness estimate that is both clinically and methodologically justifiable. These findings highlight that while uncertainty exists in PFS projections, epcoritamab remains cost-effective under a range of assumptions at a willingness-to-pay threshold of £30,000/QALY.

Table 91. Scenario analysis: Epcoritamab PFS

Epcoritamab PFS extrapolation	Total			Incremental (compared with current 4L+ care)			
	Costs	LYs	QALYs	Costs	LYs	QALYs	ICER (£/QALY)
Log-normal	██████	8.758	5.176	██████	7.018	3.994	██████
Gen. gamma	██████	8.758	5.522	██████	7.018	4.329	██████
Log-logistic	██████	8.758	5.175	██████	7.018	3.998	██████
Weibull	██████	8.758	5.043	██████	7.018	3.859	██████
Gamma	██████	8.758	4.976	██████	7.018	3.787	██████

Costs and QALYs discounted; LYs undiscounted

Severity modifier of ×1.2 applied

Base case extrapolation marked in blue text

Gen., generalised; ICER, incremental cost-effectiveness ratio; LYs, life years; PFS, progression-free survival; QALYs, quality-adjusted life years

3.11.3.5.3 Epcoritamab TTD

To understand the impact of varying the distribution used to extrapolate TTD outcomes for epcoritamab, a scenario analysis was performed varying the selected TTD distribution while preserving the base case settings for OS and PFS.

As shown in Table 92, varying the TTD extrapolation affects total costs but does not impact QALYs or LYs, as treatment discontinuation does not directly alter survival outcomes in the model. More pessimistic TTD extrapolations, such as Weibull, lead to higher total costs (██████) and a higher ICER (£██████/QALY), reflecting longer treatment duration and associated costs. Conversely, more conservative extrapolations, such as generalised gamma, result in lower costs (£██████) and a lower ICER (£██████/QALY), due to shorter projected treatment duration.

Despite this variation, epcoritamab remains cost-effective across all scenarios, with ICERs consistently below £30,000/QALY. The base-case log-normal extrapolation

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(£[REDACTED]/QALY) sits between these extremes, providing a balanced and justifiable assumption regarding treatment duration while avoiding over- or underestimation of costs.

Table 92. Scenario analysis: Epcoritamab TTD

Epcoritamab TTD extrapolation	Total			Incremental (compared with current 4L+ care)			
	Costs	LYs	QALYs	Costs	LYs	QALYs	ICER (£/QALY)
Lognormal	[REDACTED]	8.758	5.176	[REDACTED]	7.018	3.994	[REDACTED]
Generalised Gamma	[REDACTED]	8.758	5.176	[REDACTED]	7.018	3.994	[REDACTED]
Log-logistic	[REDACTED]	8.758	5.176	[REDACTED]	7.018	3.994	[REDACTED]
Gompertz	[REDACTED]	8.758	5.176	[REDACTED]	7.018	3.994	[REDACTED]
Weibull	[REDACTED]	8.758	5.176	[REDACTED]	7.018	3.994	[REDACTED]
Gamma	[REDACTED]	8.758	5.176	[REDACTED]	7.018	3.994	[REDACTED]
Exponential	[REDACTED]	8.758	5.176	[REDACTED]	7.018	3.994	[REDACTED]

Costs and QALYs discounted; LYs undiscounted

Severity modifier of ×1.2 applied

Base case extrapolation marked in blue text

ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years; TTD, time to treatment discontinuation

3.11.3.6 Applying a PFS/TTD HR to derive TTD outcomes for current 4L+ care

A scenario analysis was performed to explore the impact of applying a tailored approach that leverages the relationship between PFS and TTD observed within the HMRN dataset for modelling discontinuation of current 4L+ care. First, a HR was calculated between HMRN PFS and TTD ([REDACTED]). This HR is then applied to the HMRN PFS curve, which itself is generated by applying a MAIC derived HR to the epcoritamab PFS data, to derive the corresponding HMRN TTD curve. This method implicitly captures the impact of matching adjustment because the HR is applied to a PFS curve that reflects the MAIC-adjusted population, and by anchoring TTD to the PFS relationship observed in HMRN, this ensures that TTD is appropriately modelled within the UK clinical practice context while maintaining comparability with PFS and OS estimates.

As seen in Table 93, using this tailored approach leads to slightly lower total costs for current 4L+ care (£[REDACTED] vs. £[REDACTED] in the base case). As a result, the ICER increases Company evidence submission for epcoritamab for treating relapsed or refractory follicular lymphoma patients after three or more systemic treatments

marginally to £[REDACTED]/QALY and remains well below the £30,000/QALY threshold, confirming that epcoritamab remains cost-effective under this assumption. This analysis provides a useful sensitivity check, demonstrating that the cost-effectiveness conclusions are robust even when an HR-adjusted approach to modelling discontinuation of current 4L+ care is used instead of the raw HMRN data.

Table 93. Scenario analysis: PFS/TTD HR to derive current 4L+ care TTD

	Total			Incremental			
	Costs	LYs	QALYs	Costs	LYs	QALYs	ICER (£/QALY)
Epcoritamab	[REDACTED]	8.758	5.176	-	-	-	-
Current 4L+ Care	[REDACTED]	1.740	1.182	[REDACTED]	7.018	3.994	[REDACTED]

Costs and QALYs discounted; LYs undiscounted

Severity modifier of ×1.2 applied

ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years

3.11.3.7 Using resource use estimates from TA894

A scenario analysis was performed to explore the impact of applying the resource use estimates from TA894 in the economic analyses (Table 94).

Table 94. Resource use frequency applied in TA894

	Progression-free	Progressed disease
Haematologist visit	1 every 3.5 months	1 every 4 weeks
Diagnostic scans	1 every 3.5 months	1 every 4 weeks
CT scans	1 every year	None

Progression-free resource use is taken from the maintenance period of TA894

CT, computerised tomography

As seen in Table 95, applying these resource use estimates from TA894 reduces the ICER for epcoritamab compared with current 4L+ care through lower incremental costs ([REDACTED]), driven by less intensive resource management in the PF health state. This scenario demonstrates that epcoritamab remains a cost-effective use of NHS resources compared with current 4L+ care when different estimates of resource utilisation are applied within the analysis.

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Table 95. Scenario analysis: Resource use from TA894

	Total			Incremental			
	Costs	LYs	QALYs	Costs	LYs	QALYs	ICER (£/QALY)
Epcoritamab	██████	8.758	5.176	-	-	-	-
Current 4L+ Care	██████	1.740	1.182	██████	7.018	3.994	██████

Costs and QALYs discounted; LYs undiscounted

Severity modifier of ×1.2 applied

ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years

3.12 Subgroup analysis

There are no subgroups which should be examined separately from the main population.

3.13 Benefits not captured in the QALY calculation

New treatment option with a novel mechanism of action

As outlined in Section 1.3.6, there is no standard of care for patients with R/R FL who have received three lines of prior systemic therapy and patients currently recycle through current 4L+ care regimens to which they may already be refractory.

Recognising the short life expectancy in patients with R/R FL reaching 4L+, UK clinical experts, patients, and carers, have repeatedly expressed the need for more treatment options, an issue that has been compounded by poor availability of new and innovative medicines due to recent negative recommendations (TA892 and TA894).^{9,16,19}

Introducing epcoritamab monotherapy as a treatment option in this setting provides a valuable and novel treatment option with a new mechanism of action compared with existing treatment options and may offer increased hope and improved treatment tolerability in patients with relapsed or refractory FL.

Impact of chemoimmunotherapy regimens on HRQoL

The chemoimmunotherapy regimens used within the current 4L+ care basket are associated with severe mental and physical side effects.⁷⁰ It is therefore possible that the true impact of these side effects are not fully captured within the QALY calculation when considering the cumulative burden of toxicity (physical and psychological),

growing treatment resistance and cardiac dysfunction experienced by patients heavily

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exposed to multiple rounds of chemoimmunotherapy, as noted by clinical experts in previous appraisals.¹⁶ In addition, patients re-treated with standard therapy are likely to despair at the lack of available treatment options after three prior lines of therapy. Consequently, this would be expected to negatively impact their emotional and mental well-being, both HRQoL outcomes that could not be fully captured in the cost-effectiveness analysis.

Reduced caregiver burden and anxiety

The burden of caring for a family member with R/R FL is also not included within the QALY calculation, but presents a substantial challenge emotionally, practically and financially. Carers often provide transport to-and-from hospital appointments and treatment appointments, which can require time off work, harming personal finances and impacting societal productivity. Current 4L+ treatment regimens are administered by infusion into a vein, over the course of a few hours, presenting a significant time burden on the patient, carers and health care systems. A recent report by the Lymphoma Coalition found that 23% of individuals (carers, friends or family members) had to stop work either permanently, or temporarily, with a further 22% reporting that they had to reduce their work hours.¹⁵ Further, carers also provide emotional support while attempting to navigate an emotionally challenging situation themselves. Most also take on more chores and household tasks. The impact of R/R FL extends beyond temporal and utility burdens, with R/R diagnosis having a significant impact on the mental wellbeing of the patient and carers. Over 3 in 4 caregivers report feeling anxious and physically and emotionally worn out, with some carers and family members requiring counselling and reporting a strain on their relationships.¹⁹ Further, some carers worry that their loved one's disease has relapsed when they are ill, which can cause daily anxiety.¹⁶ Improved progression-free survival in patients treated with epcoritamab compared with current 4L+ care might introduce benefits for the carer, which are not captured within the QALY calculation.

Reduced HCRU in patients achieving complete response

As detailed in Section 2.8 and Section 2.12, patients treated with epcoritamab achieve deep and durable responses, with significantly more patients achieving CR compared Company evidence submission for epcoritamab for treating relapsed or refractory follicular lymphoma patients after three or more systemic treatments

with current 4L+ care. During clinical validation exercises, clinical experts experienced in treating patients with 4L+ R/R FL noted that patients who achieve CR would likely incur a lower healthcare resource use compared with patients who fail to achieve CR, in part due to the reduced frequency of CT/PET scans and blood tests. Due to the absence of robust estimates for HCRU in patients achieving a CR, these considerations were not applied within the economic analysis but are expected to provide a meaningful impact on patients, carers and overall healthcare system capacity.

More convenient mode of administration

The availability of epcoritamab as a subcutaneous formulation offers a more convenient mode of administration for patients, carers and healthcare delivery services.

Epcoritamab is expected to be prescribed and delivered in secondary and tertiary care settings; therefore, reduced inpatient visits and shorter appointment times will relieve healthcare system capacity and might allow clinicians to increase the number of patients they can treat per day. Whilst the cost-savings associated with subcutaneous administration compared with IV administration are captured in the economic analyses, the benefits of greater flexibility and convenience for patients, as well as the reduced capacity burden for the NHS and opportunity to optimise infrastructure with reduced numbers of IV infusions, is not fully captured. Further, patients regularly receiving IV infusions are expected to experience worsened HRQoL due to the cumulative impact of infusions compared with patients who would receive epcoritamab as a subcutaneous formulation, which is similarly not captured in the base case analysis.^{161,162} Patients with 4L+ FL can spend around [REDACTED] in inpatient hospital overnight stays due to treatment administration, monitoring and disease. Over the course of a year, this can add up to more than [REDACTED] spent in hospital with overnight stays.⁵ Despite this significant burden to patients and carers, it has not been possible to fully capture the HRQoL or resource benefit that epcoritamab, with a subcutaneous mode of administration, can offer.

3.14 Validation

3.14.1 Clinical consultations

In order to obtain clinical opinion in advance of this submission, AbbVie organised consultations with six consultant haematologists based around the UK and who are experienced in treating R/R FL with bispecific antibodies. These discussions were held in Q4 2024 and Q1 2025 and included validation of the clinical care pathway at 4L+, assessment of healthcare resource utilisation by health state and response status, selection of effect modifiers for adjustment within the MAIC and landmark survival estimates in patients treated with epcoritamab and current 4L+ care. The outputs of these discussions were implemented within the company's base case analysis and used to inform selection of survival distributions.

3.14.2 Technical validation

In alignment with best practice, validation of the economic model structure was conducted by an independent health economist prior to submission. The validation process also aimed to ensure that a high degree of transparency was maintained throughout the model and so adaptations were carried out where necessary to ensure the validity of assumptions made and methodologies undertaken within the cost-effectiveness model.

3.15 Interpretation and conclusions of economic evidence

3.15.1 Summary of evidence

In the base case analysis, epcoritamab was associated with 3.994 incremental QALYs and [REDACTED] incremental costs compared with current 4L+ care. The corresponding ICER ([REDACTED]/QALY (when applying the ×1.2 severity weighting) was comfortably within the range NICE usually considers an intervention to be acceptable use of NHS resources. These results are robust to changes in key model parameters, as evidenced in the scenario analyses where ICERs continually ran below £30,000 per QALY gained. Further, the model was robust to parameter uncertainty with the mean PSA results lying close to the deterministic results for the base-case.

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As outlined in Section 3.13, the base case analysis is unable to fully capture many of the benefits of epcoritamab to the healthcare system and patients with R/R FL, namely introducing a new treatment option for patients receiving 4L+ therapy, reduced toxicity burden compared with current therapies, and potential to improve healthcare system capacity through a more convenient mode of administration. Therefore, although epcoritamab provides a cost-effective use of NHS resources, the outcomes of this analysis are likely to significantly underestimate its full potential benefit to patients and payers.

3.15.2 Strengths and limitations of the analysis

Model structure

The model adopts a PSM structure to capture the clinical benefits of epcoritamab in patients with 4L+ R/R FL. This has the advantage of directly incorporating observed survival data from EPCORE NHL-1, reducing the uncertainty that can arise when estimating separate transition probabilities in a state-transition model and, as detailed in Section 3.2.2, this approach is aligned with previous NICE technology appraisals for R/R FL.⁹¹⁻⁹⁴

EPCORE NHL-1

The analyses presented in this submission can be considered generalisable to UK clinical practice and include outcomes data from EPCORE NHL-1 (including sites within the UK) and the HMRN registry, which collects outcomes data for patients across a large geographic region of England. To confirm the generalisability of EPCORE NHL-1 to UK clinical practice, AbbVie engaged with clinicians prior to submission to validate that the patient population enrolled within EPCORE NHL-1 resembles the characteristics of patients treated in UK practice. As part of these discussions, the clinicians noted that the overall fitness of some patients in the trial is poorer compared with standard trial populations and is well aligned with their expectations of a real-world population, albeit with higher risk features.

While EPCORE NHL-1 provides evidence for the efficacy and safety of epcoritamab as a treatment for patients with 4L+ R/R FL, it is a single-arm trial and so does not provide direct comparative efficacy evidence for epcoritamab versus current treatments in the UK. As a result, ITCs were required to generate comparative efficacy evidence, and the results of these ITCs were used to inform comparative efficacy in the cost-effectiveness model. The ITCs conducted took the form of unanchored MAICs and were conducted in accordance with NICE DSU TSD18.⁵⁸ The ITC used robust methodologies previously employed and accepted in other NICE appraisals of R/R FL treatments and adjusted for relevant and observed differences in the patient populations. However, bias due to residual confounding or unobserved differences in populations cannot be excluded.

As detailed in NICE DSU TSD14,⁷² the validity of the PHA was tested to determine whether this approach could be used to model outcomes for current 4L+ care, and concluded that the OS and PFS hazards between EPCORE NHL-1 and HMRN are proportional. Therefore, the base case analysis models the outcomes for current 4L+ care by applying a HR, reducing the number of estimated degrees of freedom compared with using independent models and thereby enhancing the precision of the long-term survival estimates.

3.15.3 Conclusions

The life expectancy for patients entering their fourth line of therapy in FL is typically short and most patients do not survive beyond one year after initiating 4L+.⁵

Epcoritamab provides hope for patients and carers alike. Analyses presented in this submission show that epcoritamab significantly extends patient life expectancy compared with current care in the UK. Additionally, patients achieve a deep and durable response with epcoritamab, offering certainty and assurance. The results of the cost-effectiveness analyses in this submission demonstrate that epcoritamab is a cost-effective use of NHS resources and represents a much-needed step change in the care of heavily pre-treated FL.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Epcoritamab for treating relapsed or refractory follicular lymphoma [ID6338]

Summary of Information for Patients (SIP)

April 2025

File name	Version	Contains confidential information	Date
ID6338_Epcoritamab_FL_ SIP_[NoCON]	1.0	No	11th April 2025

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the [Health Technology Assessment International – Patient & Citizens Involvement Group](#) (HTAi PCIG). Information about the development is available in an open-access [IJTAHC journal article](#)

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

Epcoritamab (Tepkinly®)

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

The population that will use this treatment is people with **relapsed** or **refractory** follicular lymphoma who have already received three lines of prior therapy. When a disease is relapsed, it means it that it has become worse again after a period of improvement, and when a disease is refractory it means it is not responding to treatment. Follicular lymphoma usually develops fairly slowly. However, after a patient has relapsed or become refractory to treatment and after a patient has received several treatments, the disease becomes more aggressive, with worse symptoms and poorer life expectancy.^{1,2}

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

The **marketing authorisation** is a license that enables a drug to be sold; it is only granted after assessing and reviewing all of the evidence for that drug. The marketing authorisation for epcoritamab as a treatment for **relapsed/refractory** follicular lymphoma is still pending, as described in Section 1.2 of the Company Submission.

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

AbbVie collaborates with various patient groups supporting people with follicular lymphoma.

Where this includes any Transfer of Value, for example to support the development of information for patients and their families, this is declared on an annual basis and is available at: <https://www.abbvie.co.uk/our-company/policies-disclosures.html>

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

Follicular lymphoma is a slow-growing and generally incurable, chronic type of cancer where **white blood cells** cluster together in the lymph glands. This submission focuses on patients with **relapsed** or **refractory** follicular lymphoma. Approximately 2,330 people a year in the UK are diagnosed with FL with the average age of diagnosis being 67.³

Symptoms:

The symptoms of follicular lymphoma vary between individual patients, though patients typically experience heavy sweating at night, high temperatures that come and go without cause and rapid, unexplainable weight loss.⁴ Other symptoms include swelling of lymph nodes, generally in the neck, armpit or groin and extreme fatigue.⁴ Patients with follicular lymphoma also experience high levels of anxiety and depression, especially in patients with disease relapse compared with those in **remission**.⁵

Impact on patients' and carers' quality of life:

Quality of life describes how healthy, comfortable and able to participate in and enjoy life events a person is. Patients with follicular lymphoma have a reduced quality of life compared with healthy people due to the impact of their symptoms on their daily lives.⁵ Following their diagnosis, patients with follicular lymphoma are often unable to continue working.⁶ Patients with incurable lymphomas also report anxiety around fear of relapse or progression.⁷

Current treatment options for patients with follicular lymphoma who have already received 3 or more treatments are invasive and time consuming, which further impacts a patient's and their carer's quality of life. The lengthy infusions associated with rituximab-based treatments mean that patients and their carers have to spend several hours receiving treatment at a hospital, over several days during the treatment cycle, which significantly impacts a patient's ability to participate in their normal daily life. Patients with follicular lymphoma can spend around three days per month in inpatient hospital overnight stays due to treatment administration, monitoring and disease. Over the course of a year, this can add up to more than a full month spent in hospital.⁹ Patients and carers also need to travel to and from the hospital, which may result in a financial cost, as well as taking additional time on top of the already lengthy treatment.

Outcomes:

Follicular lymphoma can develop fairly slowly, however, after a patient has relapsed or become refractory to several lines of treatment, the disease becomes more aggressive, with worse symptoms. In patients with follicular lymphoma, rates of survival decrease with each line of treatment, and so those who have been treated with several treatments after periods of remission and relapse, have worse predicted survival, than those on their first treatment.^{1,2} More than 1 in 5 patients will be treated with 4 or more treatment lines.⁸ Patient data from the UK shows that by the time patients need a fourth treatment line, their follicular lymphoma is an end-of-life disease and their **overall survival** is less than 1 year. Follicular lymphoma typically progresses in 4 months at this stage.⁹

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

The main test to diagnose lymphoma is a lymph node biopsy, where a doctor removes part or all of the swollen lymph node and sends it to a laboratory where a specialist will look at it under a microscope. The patient may also have some blood tests.^{4,10}

If a patient is diagnosed with follicular lymphoma, they may also need further tests including a PET-CT scan and a bone marrow test.^{4,10} These tests help show how much the lymphoma has grown or developed, known as 'staging' the lymphoma. Knowing the 'stage' of the lymphoma helps the healthcare team know whether a patient should start treatment and decide which treatment is right for the patient. The doctor will also consider other factors, such as a patient's age, general fitness and the results of their blood tests to determine the best treatment for each patient.^{4,10}

There are no additional tests required for epcoritamab beyond those currently in place to diagnose follicular lymphoma.

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
 - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
 - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

Patients with follicular lymphoma often go through cycles of treatment, where they stop responding to one treatment and so are given a different treatment. Each one of these treatments is known as a treatment line, with the first treatment being the first **treatment line**, the second treatment being the second treatment line and so on. In follicular lymphoma, there are a limited number of treatments available on the NHS. Therefore, once a patient has stopped responding to their second or third treatment line, they often have to repeat, or "recycle" a treatment they have been treated with before, even though this treatment may be less effective the second time round or they have already failed to respond well to it the first time.

Some patients with follicular lymphoma will be eligible for a stem cell transplant. This procedure replaces damaged or destroyed stem cells in the bone marrow with healthy ones and may cure a patient's follicular lymphoma. Patients may receive a transplant as their second or third treatment line. However, this is an intensive treatment with more side effects than other treatment options, and so is only offered to those considered medically fit enough.¹¹

There is no defined treatment pathway for patients with follicular lymphoma, especially as patients need more treatment lines. If a patient fails to respond to their first treatment or stops

responding, there is no defined second, third or fourth treatment. Instead, a clinician will consider what the patient has been treated with before. If a patient still responds to rituximab, then NICE currently recommends rituximab-based treatments, either rituximab with chemotherapy or rituximab with lenalidomide.

Rituximab is a targeted therapy, which binds to a specific protein on the surface of **white blood cells** called CD20. It is given as an infusion into a vein or an injection into the skin (after at least one infusion). The first infusion is given slowly to reduce any reactions to the drug, with later infusions given over shorter periods of time. Rituximab may be given with chemotherapy, known as **R-CHOP** (rituximab with cyclophosphamide, doxorubicin, vincristine and prednisolone), **R-CVP** (rituximab with cyclophosphamide, vincristine and prednisolone) or **R-Benda** (rituximab with bendamustine), depending on the chemotherapy drugs used. Rituximab may also be given with lenalidomide, another targeted cancer therapy which blocks the development of new blood vessels that cancer cells need to grow.

If a patient was previously treated with rituximab and no longer responds to this treatment, then NICE recommends treating them with obinutuzumab with bendamustine. Obinutuzumab is another monoclonal **antibody** that targets the CD20 protein on the surface of white blood cells. Obinutuzumab is also given as an infusion into a vein.

A diagram of the current treatment pathway for patients with follicular lymphoma is provided in Figure 1.

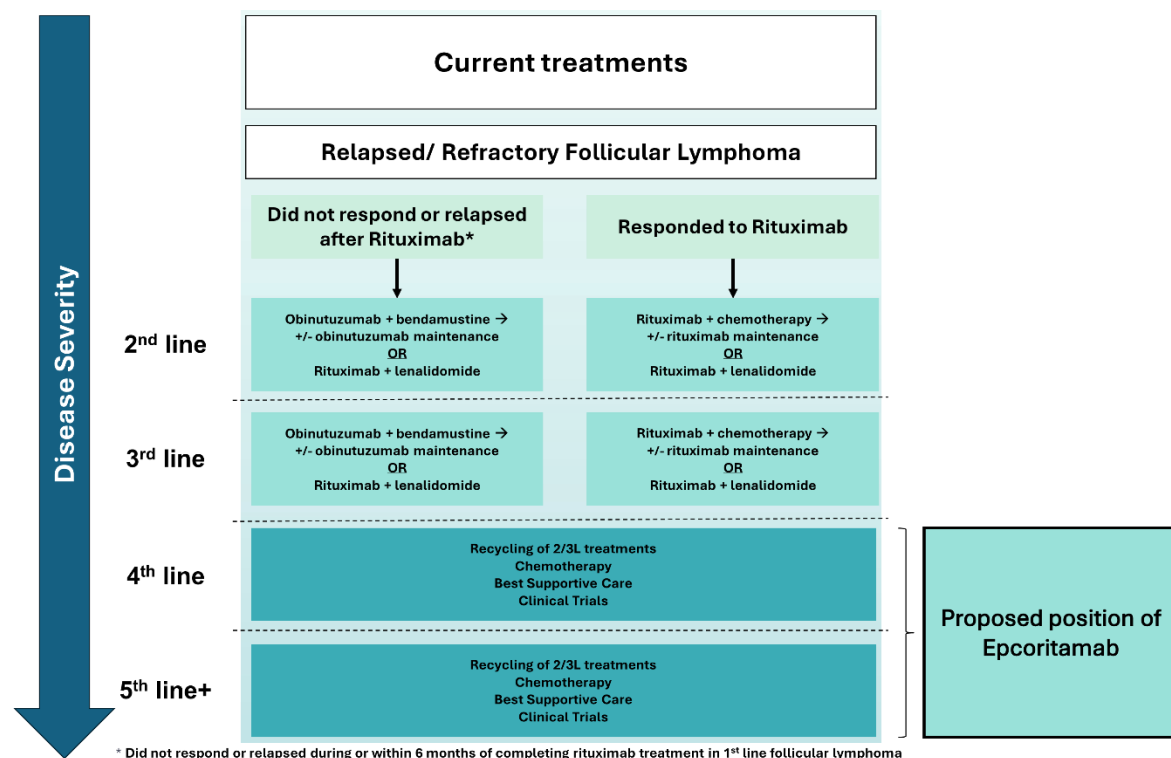


Figure 1: current treatment pathway for relapsed or refractory follicular lymphoma

All of the current treatments offered to patients require frequent hospital visits, with lengthy treatment administration and frequent monitoring.⁹ This places a considerable burden on both patients and carers, and can provide challenges due to the time required for each treatment,

which may prevent both the patient and carer from working or pursuing their normal daily activities.

There are currently no treatments specifically recommended for fourth line treatment of follicular lymphoma and patients often have very limited treatment options at this stage beyond reusing a treatment that they have already been treated with and stopped responding to. All current treatments work in a similar way by binding to the CD20 protein on the cancer cells or as a chemotherapy. As such, by the time patients need a fourth treatment line, their **overall survival** is less than 1 year in the UK.⁹ Despite this, there have been limited innovations in recent years that have met the standard to be recommended by NICE in this patient population, with no positive recommendations made since 2020. Epcoritamab would meet a significant unmet need in this patient population, by offering a new treatment for patients that works in a different way to previous treatments.

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

This section summarises some of the key findings from published studies on the impact of follicular lymphoma on patients and their ability to lead their normal lives. A study where patients with follicular lymphoma were asked to complete a survey about their health, work life and normal activities, found that following their diagnosis, patients with follicular lymphoma are often unable to continue working.⁶ Patients also reported that they could not do over half of their normal daily activities.⁶ The patients reporting a poor overall health status and those receiving systemic therapy had the greatest reduction in ability to work and perform normal daily activities.⁶

AbbVie recently carried out a study to understand the patient experience of living with follicular lymphoma.¹² This study involved asking 15 clinicians and 13 patients or carers from the UK, Germany and Japan about their experiences during 60 minutes interviews.¹² Patients with later stage follicular lymphoma, who were on their second or later lines of treatment, reported feeling disappointed, exhausted and dismayed that they needed to restart treatment. Patients with follicular lymphoma reported experiencing shock at their diagnosis and that they lived with high levels of anxiety over the fear of the disease returning.¹²

The Lymphoma Coalition, a non-profit organisation comprised of a worldwide network of patient advocacy groups that supports those affected by lymphoma, conducted a web-based global survey asking patients with lymphomas or chronic lymphocytic leukaemia (CLL), including those with follicular lymphoma, about their experiences.¹³ When asked about their overall well-being, 35% of patients experienced problems with loss of strength, 32% experienced anxiety and/or depression and 22% experienced pain or discomfort over the past months. Patients also reported issues with walking, washing or dressing and fine motor skills, demonstrating the broad impact that lymphomas have on every aspect of a patient's daily life. Over half of patients (54%) reported that they were unable to do their usual activities without difficulty.¹³

During the same survey, 46% of patients reported that they feared relapse or progression during the past 6 months. Similarly, 57% of caregivers, including friends and family members of patients with CLL, reported that they feared disease progression or relapse, with 51% reporting that they felt worried, and 49% reporting anxiety or nervousness. Almost half of caregivers also reported that they had to stop working, either temporarily, permanently or reduce their working hours since the patient was diagnosed.¹³

The current rituximab-based treatments available to patients require lengthy infusions with regular visits to hospitals for these appointments, which may last for several hours.^{11,14} Recent data have showed that patients may spend more than a month each year in inpatient hospital overnight stays by their fourth line of treatment for follicular lymphoma.⁹ Administering treatment for follicular lymphoma presents a substantial burden for patients and caregivers and there is demand for new therapies that can be more easily administered. A study asking patients with follicular lymphoma being treated with rituximab whether they preferred to have their treatment via injection or infusion found that patients preferred an injection and that patients had greater satisfaction with the injected version of the treatment.¹⁵

Patient-based evidence has shown that there is a high unmet need for a tolerable and effective alternative treatment that can help relieve patients and carers of the burden with current treatments in follicular lymphoma.

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

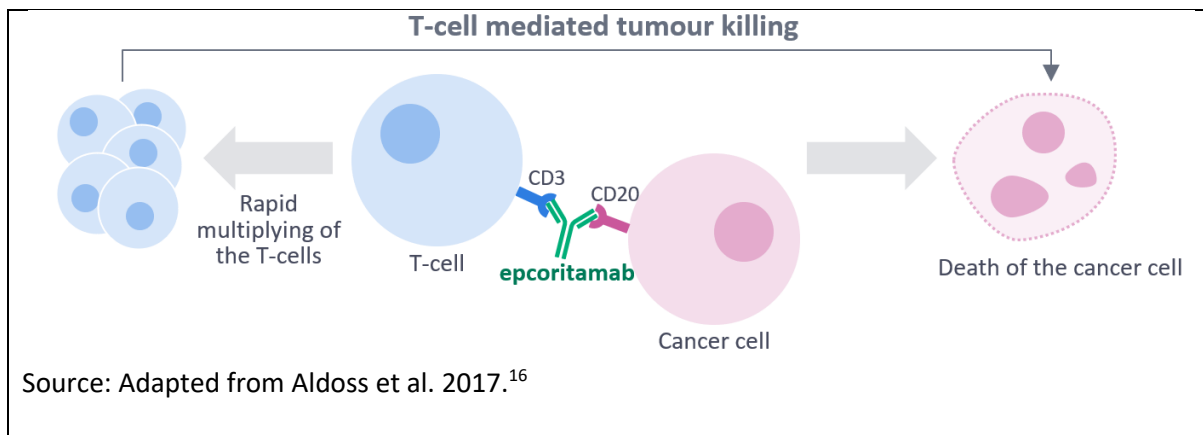
Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

Epcoritamab is injected under the skin (subcutaneous) and is a type of protein called a T-cell specific **antibody** which travels in the blood and binds to specific proteins on the surface of other cells in the body. Specifically, epcoritamab is a bispecific antibody and so is specially designed to bind to two target proteins on the surface of other cells: CD20 on the surface of B-cells (the cancer cell), and CD3 on the surface of T-cells (a type of immune cell).

When epcoritamab is attached to both CD3 and CD20, the immune cell and the cancer cell are brought closely together. Binding of epcoritamab to CD3 also causes the immune cell to make multiple copies of itself which then target and kill the cancer cell.



3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- Yes / No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

Not applicable - epcoritamab is not intended to be used in combination with any other medicines when treating patients with **relapsed** or **refractory** follicular lymphoma in this indication.

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

Epcoritamab is given as an injection under the skin (subcutaneous), by either a doctor or nurse, preferably in the lower part of the abdomen or thigh.¹⁷ This means that each injection requires the patient to visit a hospital as an **outpatient**. However, the injection itself should be fairly quick, offering more convenience to patients than rituximab-based therapies, which require lengthy infusions.

Treatment with epcoritamab is given in cycles, where each cycle lasts 28 days. In the first three cycles, epcoritamab is given once a week, which decreases to once every two weeks for cycles 4-9 and then only once every four weeks after that. The dose is increased from 0.16 mg in the first injection, to 0.8 mg in the second injection, 3 mg in the third injection, followed by 48 mg for every injection after that.¹⁷ The dosing schedule is summarised in the table below (Table 1).

Patients receive epcoritamab until disease progression or until they need to stop treatment due to the severity of any side effects.

Table 1: epcoritamab dosing schedule

Cycle	1				2 and 3				4 to 9		10+
Day of Cycle	1	8	15	22	1	8	15	22	1	15	1
Dose (mg) ^a	0.16	0.8	3	48	48	48	48	48	48	48	48

In comparison, rituximab-based treatments, are given by an infusion into a vein, which is given slowly over a few hours for the first treatment to prevent side effects.¹⁴ Patients treated with rituximab-containing treatments should have a blood test either the day of, or the day before treatment, and so may require two trips to a healthcare setting.¹⁴ Some patients may receive rituximab as an injection into the skin, if they have already completed one cycle as an infusion.¹⁴

Patients who are given rituximab with lenalidomide take a lenalidomide tablet every day for the first 21 days of a 28 day cycle, with a seven day rest period.¹⁸ They also receive a rituximab infusion into a vein once per week during their first treatment cycle, and then once every four weeks for the next 2-5 cycles. Each infusion will require a visit to a clinical setting.

Due to the infusions into veins required for rituximab-based treatments, these treatments require either a temporary tube to be put into a vein in the patients arm or hand (cannula) to be fitted for each treatment or a longer term tube to be inserted,¹⁴ which often requires surgery and can be uncomfortable for patients. This is not needed for epcoritamab.

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

The EPCORE NHL-1 (NCT03625037) Phase 1/2, multi-national trial provides evidence for how effective epcoritamab treatment is in patients with **relapsed or refractory** follicular lymphoma after two or more lines of treatment.¹⁹ The trial also provides evidence on the safety profile of the treatment. Most of the patients in the EPCORE NHL-1 trial were from Europe and 9% were from the UK.¹⁹ In this submission, we have focussed on the patients who had previously received 3 or more lines of therapy, as this is where there is the greatest clinical unmet need and where follicular lymphoma is an end-of-life disease.

EPCORE NHL-1 was an open label trial, meaning that both patients and doctor knew which treatment they were receiving, and all patients were treated with epcoritamab. This study design is common in cancer trials where patients are at a late stage of their disease, as it may not be considered ethical to give patients an alternative treatment in this situation.²⁰

The EPCORE NHL-1 trial enrolled patients with several different types of B-cell lymphoma, including a follicular lymphoma cohort, which was split further into the total cohort and a cohort of patients who had failed 3 or more previous treatments and were on their fourth line treatment. There were 155 patients enrolled in the trial overall, of which, 81 patients were in the follicular lymphoma cohort who had received at least 3 or more lines of treatment previously.¹⁹

To be enrolled in the follicular lymphoma cohort with at least 3 or more prior lines of treatment, patients had to be:

- 18 years or over,
- diagnosed with follicular lymphoma,
- had relapsed, progressed or refractory disease after treatment with rituximab, and have been given all other standard treatments.¹⁹

The trial started in 2018 and the most recent data are available from April 2024. The trial is still ongoing with the final data expected in 2029.

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

Clinical Trial Results:

The effectiveness of epcoritamab to treat follicular lymphoma in patients who have already received three or more previous lines of treatment was shown in the EPCORE NHL-1 clinical trial. During this trial, all patients were given epcoritamab and so there is no direct comparison of epcoritamab with other treatments. This study design is common in cancer trials due to ethical considerations, given that patients who have received multiple lines of prior therapy have limited options and poor outcomes with currently available therapies.²⁰

During EPCORE NHL-1, most patient's follicular lymphoma had either gone away or shrunk, known as the overall response rate, after epcoritamab treatment. Over half of patients had no signs of follicular lymphoma after tests and the disease had shrunk by over 30% in a further fifth of patients, meaning over 80% of patients had a clinically meaningful response to epcoritamab treatment.¹⁹ Three years after starting epcoritamab treatment, over half of the patients in the trial were still alive and almost half of patients were still progression free. More details on the results of the EPCORE NHL-1 trial can be found in Section 2.8 of the Company Submission.

Epcoritamab compared with other available therapies:

As the EPCORE NHL-1 trial only treated patients with epcoritamab, there is no direct evidence comparing how well epcoritamab works with current care in England. To assess this, a statistical analysis was conducted, where patients' response and survival after epcoritamab treatment was compared with data from the Haematological Malignancy Research Network (HMRN) where patients were treated with a variety of chemotherapy-based treatments. The analysis was conducted according to NICE guidelines.

The HMRN is a network established in 2004 by researchers and NHS clinicians working across 14 hospitals in the North of England. The dataset from HMRN provides a UK-specific dataset regarding health outcomes for patients with blood cancers, including follicular lymphoma.

The results of this analysis demonstrated that patients treated with epcoritamab had significantly better rates for complete response (disappearance of all signs of cancer) and overall response (patients whose cancer has shrunk or disappeared after treatment), than patients who received existing treatments available on the National Health Service (NHS) in the HMRN data set. The analysis also predicted that patients treated with epcoritamab had significantly better **overall survival** and **progression-free survival** (the time between treatment and the cancer starting to grow again), than those treated with current treatments in the HMRN data set.

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs)**.

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

The EPCORE NHL-1 clinical trial recorded data on how epcoritamab treatment impacts a patient's quality of life with follicular lymphoma. It did this by using two questionnaires.

- The FACT-LymS questionnaire is a tool designed to assess the health-related quality of life in patients with lymphoma, by evaluating physical, emotional, and social aspects affected by the disease and treatment.
- The EQ-5D-3L is a standardised instrument that is also used to measure health-related quality of life. It features three levels of severity across five areas of health and living: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.

During the EPCORE NHL-1 trial, quality of life assessed by the FACT-LymS questionnaire was shown to be stable after epcoritamab treatment. Quality of life, assessed by the EQ-5D-3L questionnaire, was slightly improved with epcoritamab treatment.

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

The EPCORE NHL-1 clinical trial recorded safety events, including any side effects of the treatment or any unrelated patient sickness.

The most common safety event was cytokine release syndrome,¹⁹ which is when the immune system reacts too aggressively, resulting in patients developing a fever, nausea, fatigue and body aches. It is a common response to many monoclonal **antibody** or immunotherapy treatments. Prompt treatment is required to manage symptoms, however, as this is a common side effect of antibody therapy, clinicians are becoming more familiar with monitoring for and treating this response to treatment. In practice, dosing of epcoritamab has been designed to reduce the risk of cytokine release syndrome (with the introduction of an additional small dose of epcoritamab shortly after initiating treatment).

After this the most common safety events in the EPCORE NHL-1 trial were COVID-19, injection site reactions, fatigue, diarrhoea, fever, cough and low **white blood cell** count. Of these, only cytokine release syndrome and injection site reactions were deemed to be related directly to epcoritamab treatment.¹⁹

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

There is a lack of effective treatment options in relapsed or refractory follicular lymphoma; after three prior lines, patients will typically be offered another intensive chemotherapy-based regimen:

Currently there are very limited treatment options in patients with follicular lymphoma who have been treated with 3 or more previous treatments and still have active disease. Available treatment options mostly include cycling through treatments that have already previously been used in earlier lines of therapy and in many cases failed to give a long-term response. Epcoritamab would offer these patients a new treatment option at this late stage of the treatment pathway. As epcoritamab works in a different way to the treatments offered earlier after diagnosis, this provides greater treatment choice and a new way to treat the disease.

Patients whose disease has stopped responding to treatments report greater levels of anxiety and depression compared with those whose disease is responding to treatment.⁵ Therefore, epcoritamab should help relieve some of this anxiety by offering a new treatment option to those whose disease has stopped responding to prior treatments.

Epcoritamab is an effective treatment in follicular lymphoma, extending life expectancy compared with existing UK treatments:

During the EPCORE NHL-1 trial, over half of the patients treated with epcoritamab were still alive after almost 3 years. During this time, most of the patients saw a response in their disease, with over half of patients demonstrating no signs of follicular lymphoma after tests and 20% demonstrating that the extent of their disease had decreased by 30%.¹⁹

A statistical analysis comparing epcoritamab treatment from the EPCORE NHL-1 trial with current NHS treatment options showed that patients treated with epcoritamab had significantly better rates for complete response (disappearance of all signs of cancer) and overall response (patients whose cancer has shrunk or disappeared after treatment), than patients who received current NHS treatment options in the HMRN data set. The analysis also predicted that patients treated with epcoritamab had significantly extended patient life expectancy compared with currently available treatments. The analysis showed that patients treated with epcoritamab were 75% less likely to die than those treated with current options.

Treatment with epcoritamab during the EPCORE NHL-1 trial was shown to be tolerable with the most common side effects of the treatment being cytokine release syndrome and injection site reactions. Cytokine release syndrome is a common response to this type of cancer treatment that is monitored for and can be treated with established guidelines.¹⁹

Epcoritamab is a subcutaneous treatment option which can provide a convenient alternative to current intravenous therapies:

Epcoritamab is the first and only subcutaneous treatment available for this patient group. This subcutaneous administration enables fast administration across different practice settings when compared with currently available intravenous therapies. Current intravenous therapies are given as an infusion and may require hospital visits on multiple days for additional monitoring. Patients may spend more than a month each year in overnight inpatient hospital stays.⁹ Epcoritamab

offers more convenience to both patients and carers as less time is required for each appointment, and therefore, this should reduce any time off from paid work or from societal commitments. These shorter appointment times will also improve the capacity of the healthcare system, allowing clinicians to increase the number of patients they see every day.

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

Epcoritamab is given as an injection under the skin, which must be given by a healthcare professional in a clinical setting, which requires the patient and their carer to visit this setting once every week for the three cycles, decreasing to once every two weeks and then once every month.¹⁷ However, this is more convenient than the current treatments used to treat late-stage follicular lymphoma, which are given as an infusion which also require a visit to a healthcare setting and take a long time to administer.^{14,18}

The main side effects of epcoritamab treatment are cytokine release syndrome and injection site reactions.¹⁹ More than half of patients reported having cytokine release syndrome after starting epcoritamab treatment, which may have resulted in a fever, nausea, fatigue and body aches. However, all of these cases were low-grade (Grade 2 or below), and so not considered severe, and could be easily managed. These side effects are a common response to this type of cancer treatment that is monitored for and can be treated with established guidelines.

During the EPCORE NHL-1 trial, a group of patients were treated with three lower doses of epcoritamab before receiving the full dose, which is the same dosing schedule as patients would receive if epcoritamab were approved. When patients were treated with these earlier doses fewer patients experienced cytokine release syndrome and these were mostly grade 1 and considered mild. The most common safety events were COVID-19, injection site reactions, fatigue, diarrhoea, fever, cough and low **white blood cell** count. Of these, only cytokine release syndrome and the injection site reactions were deemed to be related directly to epcoritamab treatment.¹⁹

3i) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

The economic model and how does it reflect follicular lymphoma?

An economic model has been used to assess the value of epcoritamab for patients with follicular lymphoma to the NHS. The economic model estimates long-term clinical and economic cost benefits (**cost effectiveness**) of epcoritamab compared with currently available treatments for patients with follicular lymphoma who have received three or more lines of therapy.

The model considers three patient groups:

- patients who are progression-free, including patients who are alive and whose disease has not progressed,
- patients with progressed disease, who are alive and whose disease has progressed
- patients who have died from either follicular lymphoma or other causes.

The movement of patients between these groups reflects a patient's real-world experience as their cancer progresses, or is delayed from progressing as a result of an effective treatment. Movement between the groups is modelled using probabilities calculated using survival and progression data from the EPCORE NHL-1 trial and the HMRN data set, which shows the effect of currently available treatments used in the NHS.

All patients enter the model in the progression-free group and stay there until they progress or die. While in each group, costs are applied to each patient for the treatment, treatment administration and monitoring of the patient for their follicular lymphoma, as well as costs of any side effects from their treatment or their disease. The model considers patients over their full lifetime.

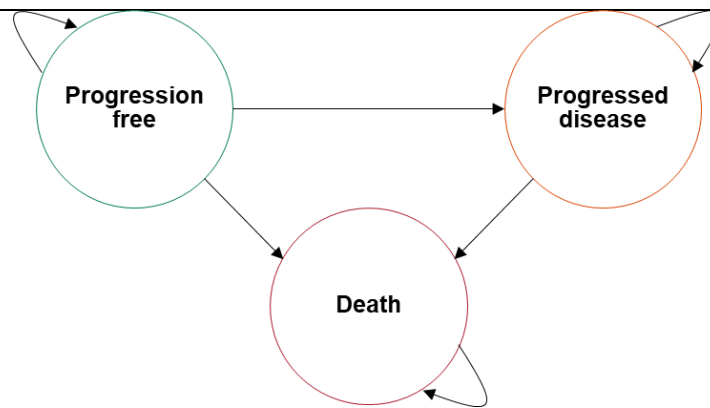


Figure 1: Overview of model structure used to assess the cost-effectiveness of epcoritamab in patients with follicular lymphoma who have received three or more previous treatments

How much does epcoritamab extend life?

As clinical trials monitor patients over a short period of time, but the effect of cancer and the potential benefits of treatment can affect patients for much longer periods, the economic model requires long-term predictions based on survival outcomes observed in the trial. The need to predict beyond the observation period of a clinical trial is common in appraisals of cancer therapies and allows the long-term effects of treatment with epcoritamab to be estimated over the remainder of a patient's life. In the economic model for this appraisal, survival outcomes were derived from the EPCORE NHL-1 trial and HMRN data set and showed a significant improvement in life expectancy for epcoritamab compared with current treatments in England. Curves for survival outcomes were extrapolated using guidance from NICE.

How much does epcoritamab improve quality of life?

The impact that treatment with epcoritamab has on patients' quality of life, in combination with how much longer they live after receiving treatment, is captured as part of a metric called **quality-adjusted life years (QALYs)**, where one QALY reflects one year in perfect health. **QALYs** are a health outcome measure that consider both the length and the quality of life provided by a treatment.

Data related to quality of life was also collected in EPCORE NHL-1 using the EQ-5D-3L questionnaire filled out by patients in the EPCORE NHL-1 trial. Overall, **QALYs** improved in people who received epcoritamab compared with people who received chemoimmunotherapy, reflecting a comparative improvement to patient's length of life and quality of life after receiving treatment.

How does the model estimate the cost of epcoritamab and its comparators?

The economic model estimates the costs associated with medication, including epcoritamab and current care in England and how these treatments are administered. For example, costs are applied for each infusion or injection based on published NHS costs, which account for the nurse's time. In addition, costs associated with how follicular lymphoma is managed and monitored, which depends on response to treatment and any side effects or other health events, which are dependent of disease progression are included in the model.

Is there any uncertainty in the model?

During the development of an economic model, companies are required to make assumptions where there is a lack of available evidence. For this model, there was little published literature to inform some of the assumptions, especially data from clinical trials. Instead, some of the assumptions were informed by evidence from real-world clinical practice, which was collected with less well-controlled conditions. Likewise, as patients only received epcoritamab in the EPCORE NHL-1 trial, there was no direct comparison to another comparator, and so the economic model relies on the results of the “unanchored” comparison. These assumptions were tested through sensitivity analyses, where alternate assumptions or values were used in the economic model to determine the impact on the economic results.

The results of the sensitivity analysis were comparable to the base-case analysis, showing that the economic analysis is robust.

Are there any additional factors to consider?

The current treatments that patients receive after their third line of therapy are associated with intense mental and physical side effects. Some of these side effects, such as the increased risk of heart disease after repeated **R-CHOP** treatment,²¹ place a considerable physical burden on the patients and are difficult for the NHS to treat. These side effects were not fully considered in the economic modelling during this submission due to a lack of treatment-specific data. The introduction of epcoritamab to this treatment pathway should help reduce the mental and emotional burden to patients compared with re-treatment with a therapy a patient may have already failed to respond to.

It is also difficult to capture in the model the quality of life impact that a treatment given by an injection has compared with a treatment given by infusion. This is because it is hard to quantify how these treatments impact a patient’s quality of life and so the convenience that epcoritamab offers patients compared with current treatments that are given by an infusion, are not included in the model. Likewise, it is difficult to quantify any benefits to a patient or a carer’s mental health due to the availability of another treatment at a stage when current treatment options are limited to often recycling a treatment the patient has previously failed to maintain a response to. Therefore, the model does not consider the emotional benefit of new treatments becoming available.

The economic modelling conducted during this submission did not consider the burden of caring for a friend or family member with follicular lymphoma on caregivers, as this is not considered by NICE in their decision making. These caregivers face considerable emotional, practical and financial challenges. Carers often provide transport to-and-from hospital appointments and treatment appointments, which can require time off work and social productivity. Carers also provide emotional support while trying to deal with the emotions surrounding a loved one being seriously ill. Improved response rates and **progression-free survival** in patients treated with epcoritamab could significantly reduce the burden on caregivers, as would the knowledge that alternative treatment options are available to patients who fail to respond to the early treatment lines.

3j) Innovation

NICE considers how innovative a new treatment is when making its recommendations. If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

Epcoritamab would represent an important advancement in the treatment of follicular lymphoma

Currently, there is no standard treatment for patients with follicular lymphoma who have failed to maintain a long-term response after three or more previous treatments. These patients instead cycle through previous treatments, which they may have already stopped responding to, resulting in life expectancy in these patients being less than 1 year.⁹ Current treatment options for patients involve lengthy infusions given through invasive ports or cannula, and the time required for each administration places a huge burden on patients and carers.

Introducing epcoritamab would offer these patients a new treatment option, which works in a different way to the treatments that these patients have previously failed to respond to and so may offer increased hope and be more tolerable, while also providing improved survival rates.

3k) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics

More information on how NICE deals with equalities issues can be found in the NICE equality scheme [Find more general information about the Equality Act and equalities issues here](#)

It is not anticipated that the provision (or non-provision) of epcoritamab within its licensed indication would exclude from consideration any people protected by equality legislation, lead to a recommendation that has a different impact on people protected by equality legislation or lead to recommendations that will have adverse impact on people with a particular disability or disabilities.

However, patients who have stopped responding to multiple previous therapies are likelier to receive experimental treatments within clinical trials than patients in earlier lines. As access to clinical trials might be more restricted in rural or deprived areas, the patient population in this appraisal would be likely to benefit from access to an efficacious therapy as part of routine commissioning.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc. Where possible, please provide open access materials or provide copies that patients can access.

Further information on follicular lymphoma may be found here, including the different treatments currently available:

- [Follicular lymphoma | non-Hodgkin lymphoma \(NHL\) | Cancer Research UK](#)
- [Follicular lymphoma | Lymphoma Action](#)
- [Treatment for non Hodgkin lymphoma | Cancer Research UK](#)
- [Follicular lymphoma - what is it, symptoms and treatment | Blood Cancer UK](#)

Further information on epcoritamab may be found here:

- [Epcoritamab \(Tepkinly®\) | Macmillan Cancer Support](#)

Information on the EPCORE NHL-1 trial may be found here:

- [Epcoritamab monotherapy in patients with relapsed or refractory follicular lymphoma \(EPCORE NHL-1\): a phase 2 cohort of a single-arm, multicentre study - The Lancet Haematology](#)
- [Study Details | First-in-Human \(FIH\) Trial in Patients With Relapsed, Progressive or Refractory B-Cell Lymphoma | ClinicalTrials.gov](#)

Further information on NICE and the role of patients:

- Public Involvement at NICE [Public involvement | NICE and the public | NICE Communities | About | NICE](#)
- NICE's guides and templates for patient involvement in HTAs [Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector \(VCS\) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE](#)
- EUPATI guidance on patient involvement in NICE: <https://www.eupati.eu/guidance-patient-involvement/>
- EFPIA – Working together with patient groups: <https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf>
- National Health Council Value Initiative. <https://nationalhealthcouncil.org/issue/value/>
- INAHTA: <http://www.inahta.org/>
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

Antibody: a protein in the blood that helps the body's defences by identifying and attaching specific foreign substances including germs

Cost-effectiveness: how effective a drug is in relation to its cost

Follicular lymphoma: a form of non-Hodgkin lymphoma that forms in the lymph nodes, bone marrow and other organs. It is considered an incurable, chronic, life-limiting illness.

Marketing authorisation: a license that enables a drug to be sold; it is only granted after assessing and reviewing all of the evidence for that drug

Outpatient: a hospital appointment that does not require an overnight stay

Overall survival: the length of time from starting treatment that a patient is still alive

Progression-free survival: the time between treatment and the cancer starting to grow again

Quality-adjusted life years (QALYs): a unit to measure both the quality of life lived after receiving a treatment and how much additional life that treatment might result in

R-Benda: a chemotherapy regimen containing both bendamustine and rituximab given by infusions every 28 days

R-CHOP: a chemotherapy regimen containing rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone

R-CVP: a chemotherapy regimen containing rituximab, cyclophosphamide, vincristine and prednisolone

Refractory: when a disease has stopped responding to treatment

Relapsed: when a disease has become worse again after a period of improvement

Remission: when the symptoms of a disease have become less severe and are not affecting the patient

White blood cells: cells in the immune system that protect the body from infectious diseases and foreign invaders.

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

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16. Aldoss I, Bargou RC, Nagorsen D, et al. Redirecting T cells to eradicate B-cell acute lymphoblastic leukemia: bispecific T-cell engagers and chimeric antigen receptors. *Leukemia*. 2017;31(4):777-87.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Epcoritamab for treating relapsed or refractory follicular lymphoma after 2 or more systemic treatments [ID6338]

Clarification questions

May 2025

File name	Version	Contains confidential information	Date
ID6338_Epcoritamab_FL_CQs_ [REDACTED]	Redacted	No	22 May 2025

Section A: Clarification on effectiveness data

A1. Can the company provide real-world evidence to support the claim that the greatest unmet need lies in 4L+ FL patients?

In the Company Submission, AbbVie referred to clinical feedback that highlighted the greatest unmet need is among patients with relapsed or refractory follicular lymphoma (FL) after three or more lines of systemic therapy (4L+). This is due to the poor survival outcomes at this stage of the disease, limited treatment options and reliance on clinical trials, and increased time spent in inpatient hospital settings at 4L+ FL.

Clinical feedback reflected outcomes seen in available UK real-world evidence (RWE) in 4L+ FL. The Haematological Malignancy Research Network (HMRN) dataset has shown that 4L+ FL is an end-of-life disease; most patients do not survive longer than a year (median [REDACTED]).¹ This is aligned with expectations from consultant haematologists in England – i.e. survival in practice is typically less than one year in the 4L+ setting.

In interviews with clinical experts, it had been noted that there are limited treatment options routinely available for patients with 4L+ FL in the UK. This opinion had also been noted by the professional groups in the appraisal of axicabtagene-ciloleucel (TA894).² By the time patients initiate their fourth line of therapy, they have typically exhausted the treatment options available to them. Some younger and fitter patients may be available for enrolment in a clinical trial, though there exists barriers to access for patients who live in rural or deprived areas and who may not be able to access experimental treatments. As such, patients with 4L+ FL are more likely to benefit from access to an efficacious therapy as part of routine commissioning.

Finally, at this stage of their FL, patients spend a large proportion of their time in the inpatient setting. Data from the HMRN registry showed that patients with 4L+ FL spend around [REDACTED] in inpatient hospital overnight stays due to treatment administration, monitoring and disease. Over the course of a year, this can add up to more than [REDACTED] spent in hospital with overnight stays.¹ Indeed, the burden with frequent inpatient visits on caregivers has been noted by Lymphoma Action in a previous appraisal in 4L+ FL:²

“Carers often provide transport to-and-from hospital appointments and treatment sessions, requiring time off work... Most also take on more chores and household tasks. Over 3 in 4 caregivers report feeling anxious and physically and emotionally worn out. Some carers and family members report needing counselling.”

Given that the 4L+ FL patient population is also inclusive of patients with four or more lines of prior therapy, it stands to reason that the greatest unmet need lies within this group of patients.

A2. Why was the 4L+ patient population chosen as the focus when the NICE final scope allows for 3L+? Please provide details of the expertise of the clinicians used to justify the 4L+ unmet need.

As noted in response to Question A1, the 4L+ patient population was chosen as the focus of the NICE submission as it is the population with the greatest unmet need. The unmet need in 4L+ FL is substantial and has been validated by multiple consultant haematologists who are active in academic research and situated in NHS sites across the UK. Of the consultant haematologists interviewed, all five had previous experience treating 4L+ FL and all had observed the outcomes seen in the HMRN UK real-world evidence reflected in their practice; i.e. that survival is typically less than a year (■■■ months).¹

Specifically, during UK clinical expert interviews conducted by AbbVie, NHS consultant haematologists noted that there is no standard of care in 4L+ FL and there are limited treatment options due to relapse and increasing refractoriness to conventional treatment. Similar observations had also been made by the professional groups in the appraisal of TA894.² Patients are often rechallenged with previously administered treatments. Clinical experts noted that patients rechallenged with a prior treatment regimen often experience poor outcomes due to acquired treatment resistance. This is particularly the case if the previous therapy resulted in a non-durable remission. Given the current lack of treatment options at 4L+, clinical trials are also considered for younger and fitter patients at this stage. Accordingly, UK experts stressed the desperate need for new and innovative therapies that are routinely commissioned.

A3. Does the company plan to submit additional data for the 3L+ FL population in the future?

AbbVie can confirm that there are no plans to submit additional data for epcoritamab monotherapy in 3L+ FL.

A4. Priority Question: Please provide a CSR relating to the FL Grade 1-3A 4L+ subgroup of EPCORE NHL-1, which is the focus of the submission. Please also provide any publications or other reports of this subgroup.

AbbVie do not have a clinical study report for the 4L+ subpopulation of EPCORE NHL-1. However, as part of its original submission, AbbVie shared a document of tables and figures which reported baseline characteristics, efficacy and safety outcomes from EPCORE NHL-1. AbbVie has now provided an abbreviated version of this document (in the reference pack) which contains the formal tables, listings and figures for the key characteristics and outcomes for the 4L+ subpopulation.³ There are no publications reporting outcomes for the 4L+ subgroup of EPCORE NHL-1.

A5. Priority Question: For completeness, please provide summary efficacy and adverse event data for the subgroup FL Grade 1-3A 3L, n=47 of the expansion part of EPCORE NHL-1.

AbbVie does not intend to submit data for the 3L FL population as it does not align to the proposed population relevant for decision making. However, for completeness, the company provided efficacy and adverse event data for the 3+ FL overall trial population in Appendix M of the Company Submission. This population is inclusive of the 3L FL subgroup and as such, efficacy and adverse event data are reflected in the 3L+ outcomes.

A6. Please provide an explanation as to why the cycle-1 data only are reported for the EPCORE NHL-1 optimisation part.

The terminology 'C1-Optimisation' refers to the optimised step-up dosing schedule within the first cycle of epcoritamab treatment, which aimed to identify a dosing strategy with reduced incidence and severity of immune-mediated events including cytokine release syndrome (CRS) and immune cell associated neurotoxicity syndrome (ICANS). Specifically, the dosing regimen consisted of an initial priming

dose of 0.16 mg (C1D1) followed by a first intermediate dose of 0.8 mg (C1D8) and a second intermediate dose of 3 mg (C1D15), and a full dose of 48 mg on C1D22. This dosing regimen is aligned with the anticipated marketing authorisation for epcoritamab for patients with R/R FL. Outcomes data for the optimisation part of EPCORE NHL-1 are presented in the Section 2.14 of the Company Submission in accordance with the reported follow-up durations.

A7. Please provide an explanation for, and any available data regarding, the abandoned arm of the cycle 1 optimization cohort (Arm B), which was dropped due to there being numerically lower rates of cytokine release syndrome (CRS) in Arm A. The 'C1-Optimisation' cohort was enrolled into the EPCORE NHL-1 trial in order to evaluate alternative priming and intermediate dose regimens of epcoritamab in patients with FL. The cohort initially consisted of two arms, Arm A and Arm B, whereby 6 patients had been recruited into each arm. On the [REDACTED], preliminary analysis revealed a numerically lower CRS rate in Arm A as compared to Arm B, which was supported by modelling. In addition, the simpler instructions for the 3 mg dose preparation as compared to the 6 mg dose preparation, which requires the use of two 4 mg/0.8 mL vials, was taken into consideration, and further enrolment in Arm A was then prioritised in the FL optimisation cohort.

A8. Priority Question: For completeness, please provide summary efficacy and adverse event data for the subgroup FL 3L, n=45 of the optimisation part of EPCORE NHL-1.

As detailed in response to Question A5, AbbVie does not intend to submit additional data for the 3L FL subgroup. For completeness, the company provided efficacy and adverse event data for the 3L+ FL overall trial population from the 'C1-optimisation' part of EPCORE NHL-1 in Appendix M of the Company Submission.

A9. Priority Question: Please provide Grade 3+ AEs used in the model for the LBCL and MCL populations

The EPCORE NHL-1 trial (NCT03625037), was a multi-stage, multi-cohort study that provided clinical evidence for the safety and efficacy of epcoritamab as a treatment for adults with relapsed or refractory B-cell lymphomas: i.e. multiple indications including large B-cell lymphoma (LBCL), mantle cell lymphoma (MCL), and FL.

However, this NICE submission and the corresponding anticipated marketing authorisation is for the FL indication only. Therefore, in the company cost-effectiveness model, AbbVie included Grade 3 or 4 treatment emergent adverse events (TEAEs) that occurred in $\geq 5\%$ of the patients sourced from the EPCORE-NHL-1 Dose Expansion 4L+ FL cohort. LBCL and MCL populations are not relevant to the Decision Problem and as such, Grade 3+ AEs for LBCL and MCL have not been provided.

A10. In the dose expansion phase of the study, the first cycle dosing is different to the anticipated dosing: it was D1 0.16 mg; D8 0.8 mg and D15: 48 mg when the anticipated is: D1 0.16 mg; D8 0.8 mg and D15: 3 mg D 22: 48 mg (same as in the optimisation phase). CS page 45 says that the expansion phase used the recommended phase 2 dose (RP2D) but Table 10 reports 48 mg was used at “C1D15/C1D22”. Please explain

The EPCORE NHL-1 trial was conducted in three parts: a dose escalation part, an expansion part and an optimisation part. Table 1 below (adapted from Table 9 of the Company Submission) summarises the objectives of the various phases of the study.

Table 1: A summary of the objectives for the phases of the EPCORE NHL-1 trial

	Dose Escalation (Phase 1)	Dose Expansion (Phase 2)	Dose Optimisation (Phase 2)
Objectives	To determine the maximum tolerated dose (MTD) and the recommended Phase 2 dose (RP2D), as well as to establish the safety profile of epcoritamab in patients with relapsed or refractory B-cell lymphoma.	Additional patients were treated with epcoritamab, at the RP2D. The purpose was to further explore and determine the safety and efficacy of epcoritamab.	To evaluate alternative priming and intermediate dose regimens of epcoritamab in patients with: DLBCL, FL and MCL.

DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MCL, mantle cell lymphoma; MTD, maximum tolerated dose; RP2D, recommended phase 2 dose.

The purpose of the Phase 1 dose escalation part of EPCORE NHL-1 was to establish the maximum tolerated dose of epcoritamab and the recommended phase 2 dose (RP2D) of epcoritamab, while the purpose of the Phase 2 expansion part was to evaluate the efficacy and safety of epcoritamab at the RP2D. Therefore, in the Phase 2 expansion part of EPCORE NHL-1, patients received the RP2D determined by the dose Phase 1 escalation part, i.e. 48 mg epcoritamab was administered on C1D15/C1D22.

The separate Phase 2 optimisation part of EPCORE NHL-1 explored alternative step-up dosing regimens to reduce the incidence and severity of cytokine release syndrome (CRS) while retaining the efficacy and tolerability of epcoritamab observed in the expansion part. As detailed in the EU assessment report and Section 3.2.3.1 of the Company Submission, pharmacokinetic outcomes are very similar between patients who received the three step-up dose regimen and patients who received the two step-up dose regimen in EPCORE NHL-1.³

As expected, data showed transiently lower trough concentrations after the second intermediate dose in subjects with FL who received the 3-step SUD regimen compared to those after the first full 48 mg dose in subjects with FL who received the 2-step SUD regimen. Consistent with the observed data, model predictions demonstrate that the PK profiles for the 2-step and 3-step SUD regimens are similar over follow-up.**Error! Reference source not found..**

Accordingly, the dosing reflected in the EU marketing authorisation (and anticipated in the UK marketing authorisation) is in line with that used in the optimisation cohort.

A11. Priority Question: How many UK patients were there in the FL 4L+ and FL 3L+ groups of the expansion part of EPCORE NHL-1 and in the optimisation part. Please provide data specific to UK participants from the FL cohort (N=81), including baseline characteristics and outcomes.

The EPCORE NHL-1 trial was a multicentre international trial. Patients had been recruited from multiple sites globally, including the UK. In the dose expansion cohort, a total of █ patients (██%) with 4L+ FL were enrolled from sites in the UK. █ patients (██%) with 4L+ FL were enrolled from UK sites in the dose optimisation cohort. Due to the small sample size of the UK 4L+ FL cohort, it is not meaningful to draw strong conclusions from comparisons with the overall cohort. Accordingly, only the baseline characteristics had been assessed for UK patients with 4L+ FL from the dose expansion cohort. No UK data from the dose optimisation cohort were analysed due to the very small sample size (n = █).

The baseline characteristics for the 4L+ FL cohort in the dose expansion part of EPCORE NHL-1 are presented in Table 2.**Error! Reference source not found..** The patient baseline characteristics in the UK broadly resemble those for the overall 4L+

FL dose expansion cohort (n=81). Patients in the UK were marginally younger (mean age of █ years) than those in the overall 4L+ FL cohort (mean age of 64.8 years). Additionally, patients in the UK cohort were predominantly male (█%) and of white race (█%) compared with those in the overall cohort (65.4% and 63.0% respectively).

Overall, the baseline characteristics in the UK patients with 4L+ FL enrolled in the dose expansion cohort are similar to those in the overall 4L+ FL cohort. Additionally, clinical opinion has noted that these characteristics are reflective of those in clinical practice in England and Wales. As such, it can be expected that results for the overall 4L+ FL dose expansion cohort will closely parallel outcomes of those enrolled from sites in the UK and more broadly with UK clinical practice.

Table 2: Patient Baseline Demographic and Disease Characteristics – Patients with 4L+ FL from the UK in the Dose Expansion Cohort

	Expansion Part	
	4L+ FL and in the UK (N = █)	4L+ FL (Overall Cohort) ^a (N = 81)
Age at informed consent (years)		
Mean (SD)	█	64.8 (11.06)
Median	█	66.0
Min, Max	█	39, 84
Sex (at birth)		
Male	█	53 (65.4%)
Female	█	28 (34.6%)
Race		
White	█	51 (63.0%)
Black or African American	█	0
Asian	█	3 (3.7%)
Other	█	0
Not reported	█	27 (33.3%)
BMI (kg/m²) category at baseline		
<18.5	█	1 (1.2%)
18.5 ≤ 25.0	█	39 (48.1%)
25 ≤ 30	█	27 (33.3%)
≥ 30.0	█	14 (17.3%)
ECOG Performance status		

0		40 (49.4%)
1		38 (46.9%)
2		3 (3.7%)
Baseline renal function classification by Cockcroft- Gault method (CrCl)[mL/min]		
Normal (≥ 90)		27 (33.3%)
Mildly impaired ($60 \leq 90$)		38 (46.9%)
Moderately impaired ($30 \leq 60$)		16 (19.8%)
Severe impairment		0
Baseline hepatic function per NCI criteria		
Normal		65 (80.2%)
Mild Dysfunction		16 (19.8%)
Moderate dysfunction		0
Severe dysfunction		0
Disease type at trial entry		
FL Grade 1-3A		81 (100%)
Histological grade		
1		9 (11.1%)
2		45 (55.6%)
3A		27 (33.3%)
Not applicable		0
Median time for initial diagnosis to first dose ^b (years)		0
FLIPI		
0-1		11 (13.6%)
2		13 (16.0%)
≥ 3		57 (70.4%)
Unknown		0
Not applicable		0
Number of Prior Lines of Therapy		
Median		3.0
1		0
2		0
3		41 (50.6%)
≥ 4		40 (49.4%)
POD24		
Progression, transformation or relapse within 24 months of initiating first-line immunochemotherapy		30 (37.0%)
Double refractory to anti-CD20 and alkylating agents, regardless of two		60 (74.1%)

treatments being in the same or different treatment lines		
Bone Marrow Involvement		
Bone marrow involvement at baseline by investigator	██████	26 (32.1)

Data cut ██████, assessed by independent review committee

a. Overall cohort includes all patients enrolled in the Dose Expansion study with 4L+ FL, including patients from the UK.

b. Time from diagnosis of disease recorded at time of study entry.

BMI, body mass index; CrCl, creatinine clearance; ECOG, Eastern cooperative oncology group; FL, follicular lymphoma; FLIPI, follicular lymphoma international prognostic index; NCI, National Cancer Institute; POD24, progression of disease 24 months; SD, standard deviation

A12. Was a central pathological review performed to confirm FL grade 3A? If so, please provide detailed pathological grading for enrolled patients, including: blast count per high-power field (HPF), patterns of centroblasts with intermingled centrocytes, and presence of pure sheets of blasts.

A central pathological review was not performed to confirm FL grade 3A. Each site was required to have local histologic confirmed FL 1-3a on diagnosis as an inclusion criteria. Regardless of this approach, clinical opinion noted that outcomes in 4L+ FL would not be meaningfully different between FL grade 1-3a due to the significant unmet need after multiple prior lines of therapy and poor survival outcomes.

A13. In CS Table 9, the 'Cohorts' row suggests that in phase 2, all 3 cohorts have aNHL (ie that the iNHL cohort is a subgroup of aNHL). Section 2.4.1 suggests iNHL is separate to aNHL. Please explain.

AbbVie can confirm that there was a typographical error in the submission document and the correct language in Table 9 should read "Three Cohorts of Patients with NHL". Both iNHL and aNHL fall under the broader "NHL" patient population.

A14. The protocol for EPCORE NHL-1 excludes those with prior CAR-T therapy within 30 days of enrolment but some participants had received CAR-T therapy prior to this, does the study account for longer-term outcomes or altered disease biology in patients who previously received CAR T-cell therapy?

The protocol of the EPCORE NHL-1 study allowed for patients with prior CAR-T therapy to be recruited, though excludes those who received prior CAR-T therapy within 30 days of enrolment. Six patients who received prior CAR-T (7.4%) were included in the ITT analysis and were treated and followed up as per trial protocol. It is not expected that these patients will achieve longer-term benefit related to having prior CAR-T therapy due to relapse ahead of enrolment in the EPCORE NHL-1

study. Indeed, clinical opinion has suggested that the inclusion of patients who have relapsed following prior CAR-T therapy is indicative of a high-risk population for the EPCORE NHL-1 trial. These 6 patients were nonetheless excluded from the adjusted MAIC outcomes as “Prior CAR-T” was a variable that had been adjusted for (Table 8) and no patients were reported as having had prior CAR-T therapy in the HMRN dataset. Accordingly, this is not expected to impact outcomes from the MAIC or the cost-effectiveness model.

A15. CS Table 12 reports rates discontinuing treatment for clinical progression, please provide the definition of clinical progression used.

In FL, clinical progression is conventionally defined using the Lugano and LYRIC response criteria. Table 12 of the Company Submission records █ patients (█%) as having ‘Clinical Progression’ as the primary reason for study treatment discontinuation. As per protocol and in the majority of cases, the expected pattern of progression was recorded based on the Lugano and LYRIC response criteria. However, in rare cases, the determination of clinical progression was based on symptomatic deterioration (i.e. without documented progression through the use of objective criteria). It is not expected that patients recorded as having clinical progression by symptomatic deterioration will meaningfully differ from progression recorded by Lugano and LYRIC criteria.

A16. Please provide reasons for study treatment discontinuation labelled as ‘other’ in CS Table 12.

In Table 12 of the Company Submission, the primary reason for study treatment discontinuation had been labelled as “Other” for █ patients (█; also see Table 3 below). The specific reasons for study treatment discontinuation among each of the █ patients were recorded as follows:

1. “Maximum clinical benefit”,
2. “Investigator decision (unfavourable benefit/risk ratio)”,
3. “Medical decision due to persistent Covid positivity and disease progression due to extended treatment interruption”,
4. “Patient discontinued on principal investigator (PI) advice”,
5. “PI and patient decision as patient has been on epcoritamab drug hold since █ with sustained complete response (CR)”,

6. “Worsening of pre-existing myelodysplastic syndrome”.

A17. CS Table 12, the primary reason for study treatment discontinuation totals 103, but 68 patients discontinued treatment. Please explain

AbbVie can confirm that there was a formatting error in the submission document. As such, patients who experienced a “Clinical Progression” or “Disease Progression According to Response Criteria” could be double counted. A correctly formatted table has been provided below for clarity (see Table 3). Patients with “Progressive Disease” (n=■) include patients with a “Clinical Progression” (n=■) or “Disease Progression According to Response Criteria” (n=■).

Table 3: Patient disposition – 4L+ FL

	4L+ FL (N = 81)
Treated patients	
Ongoing trial treatment	■
Discontinued treatment	■
Primary reason for study treatment discontinuation	
Progressive disease	■
○ <i>Clinical Progression</i>	■
○ <i>Disease progression according to response criteria</i>	■
Adverse event	■
Withdrawal of subject	■
Decision to proceed with transplant	■
Other	■
Patients remaining on trial	■
Discontinued from trial	■
Primary reason for trial discontinuation	
Death	■
Lost to follow-up	1
Subject withdrew consent from trial.	■

Data cut ■
FL, follicular lymphoma

A18. Priority Question: Please provide details of how decisions over deaths attributable to Covid-19 were made, and who made the decisions, CS Section 2.6.2.1

The significant increase of COVID-19 infections and hospitalisations during late 2021 and 2022 coincided with the active treatment period of the EPCORE-NHL1 trial. As such, the number of COVID-19 related deaths does not accurately represent the current clinical setting in the UK. While the company acknowledges that there is no perfect method for capturing COVID-related deaths, given both the unprecedented nature of the pandemic and limitations resulting from a global lack of standardisation in diagnostic criteria, capacity and the presence of comorbid conditions, a conscientious approach to identifying COVID-19 related deaths was taken in the EPCORE NHL-1 trial. COVID-19 deaths were assigned as per the protocol outlined in the main trial publication⁴, namely, sensitivity analyses were conducted using a stringent criteria with evaluations and adjudications performed by physicians.

Deaths from clinically compatible illness in a probable or confirmed COVID-19 case were identified using the following criteria:

- Any death within the standardised MedDRA query of COVID-19
- Any death related to treatment-emergent adverse events (TEAEs) within system organ classes of respiratory, thoracic and mediastinal disorders
- Any death due to 'other' with COVID-19 mentioned in free text as a reason for death

These criteria have been validated by clinical experts in the UK who noted the challenges associated with defining deaths due to COVID-19 more broadly. Cases identified utilising the search strategy outlined above were reviewed for clinical plausibility by the sponsor medical reviewer. Despite the challenges associated with defining COVID-19 related deaths, the approach taken in the EPCORE NHL-1 trial is pragmatic and reflects the interpretation of UK clinical experts.

A19. CS Table 18 shows that a proportion of participants were censored for receiving 'new anti-lymphoma' therapies. Please explain how these fit in with the data presented in CS Table 22.

Table 18 in the Company Submission contains an overview of the Duration of Response (DoR) with epcoritamab in 4L+ FL. DoR has previously been defined as the time from onset of response to progression or death due to any reason.⁵ Patients initiating a new anti-lymphoma therapy (NALT) after epcoritamab treatment had been censored in assessments of DoR at the last adequate follow-up. Removing this censoring rule would create challenges interpreting whether DoR outcomes after discontinuation can be attributed to epcoritamab or the NALT. Additionally, such an approach risks overestimating outcomes for epcoritamab and creates bias. As such, patients had been censored at the last adequate assessment prior to the start of NALT.

A20. Please consider the same query above (A19) for those receiving new anti-lymphoma therapies in CS Tables 19 and 20.

Tables 19 and 20 in the Company Submission contain overviews of the Duration of Complete Response (DoCR) and PFS, respectively. As per the response to Question A19, outcomes for DoCR and PFS are at risk of bias (favouring epcoritamab) if patients beginning NALT are not censored. As such, a similar censoring rule for DoCR and PFS had been implemented to censor patients at the last adequate assessment prior to the start of NALT.

A21. Please provide details of the 'other' reasons for censoring seen in CS Tables 18, 19 and 20.

"Other" reasons for censoring patients had been included in Tables 18, 19, and 20 of the Company Submission. It can be confirmed that these reasons were attributable to censoring associated with COVID-related mortality. Outcomes excluding these "other" censoring criteria are respectively available for OS and PFS in Figure 7 of the Company Submission and in response to Question A23 below.

A22. Please provide details for the N=█ patients on 4L+ from HMRN:

- Full history of prior therapy.
- Prior therapy on year of start of 4L+ treatment.

The full history of prior therapies, inclusive of therapies prior to the year of starting 4L+ treatment, is presented in Figure 1.

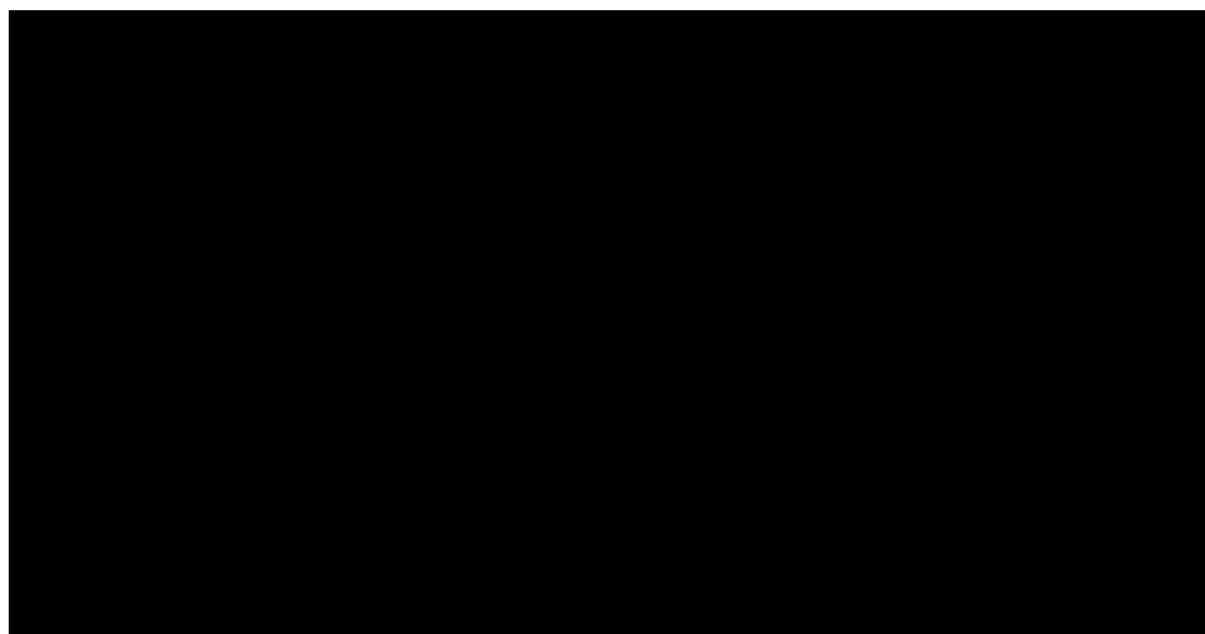
Figure 1. Sankey Diagram by treatment line from diagnosis for patients with 4L+ FL



A23. Please provide a figure for PFS similar to Figure 7 in the CS B.2.6.2 which shows the OS curves with and without adjusting for the COVID-19-related deaths, with the subjects at risk table, number of events and median PFS.

In the Company Submission, AbbVie presented OS outcomes in which COVID-related mortality had been censored. Illustrative COVID-unmodified outcomes were presented in the same figure (Company Submission, Figure 7). For completeness, the corresponding figure for PFS is provided in Figure 2; [REDACTED]. Consistent with Figure 7 of the Company Submission, a slight separation between the COVID-modified and COVID-unmodified PFS curves is observed between months 12 to 15 of trial follow-up, which is maintained throughout the remainder of the trial period. This highlights the impact of the Omicron wave of the COVID-19 pandemic on EPCORE NHL-1 survival outcomes.

Figure 2. Kaplan-Meier curves of epcoritamab PFS data demonstrating the impact of the Omicron wave of the COVID-19 pandemic



Data cut [REDACTED]

As detailed in Section 2.6.2.1 of the Company Submission, [REDACTED] of the [REDACTED] deaths attributed to COVID-19 occurred in patients who were in CR at the time of their death. This can also be seen in Figure 2, wherein the difference between the two curves is similar to that shown in Figure 7 of the Company Submission. Such patients with a CR would typically have a low risk of death and significantly extended OS compared with patients who achieve a partial response or no response. This observation has been noted by clinical experts in separate interviews. This, considered alongside Figure 31 of the Company Submission, supports the case that most patients remained progression-free and were otherwise performing well on epcoritamab at the time of their death due to COVID-19.

Indirect and mixed treatment comparisons

A24. Were sensitivity analyses conducted to assess the robustness of the ITC results? If so, please present them. If not, please justify why they were not performed.

AbbVie performed two sensitivity analyses of the MAIC to assess the robustness of the analyses to different matching assumptions, with particular focus on variables

highlighted as important by UK clinicians: ECOG performance status, FLIPI score and patients' refractory status.

Sensitivity Analysis 1 – ECOG and FLIPI

In the first sensitivity analysis, AbbVie selected variables for matching which aligned with the company base case but also explored the impact of matching for ECOG performance status 0 (i.e. patients with better health status) and FLIPI score 3,4,5 (i.e. patients with worse health status). As described in the Company Submission, both of these factors were noted by clinicians as being important prognostic indicators in FL, but reporting limitations in HMRN meant that these variables were only recorded at diagnosis, rather than at the start of initiating 4L+ treatment.

After match-adjusting the EPCORE population to HMRN, the effective sample size for epcoritamab patients is 28 (Table 4).

Table 4. MAIC sensitivity analysis 1: Baseline characteristics for epcoritamab vs HMRN in 4L+ indication

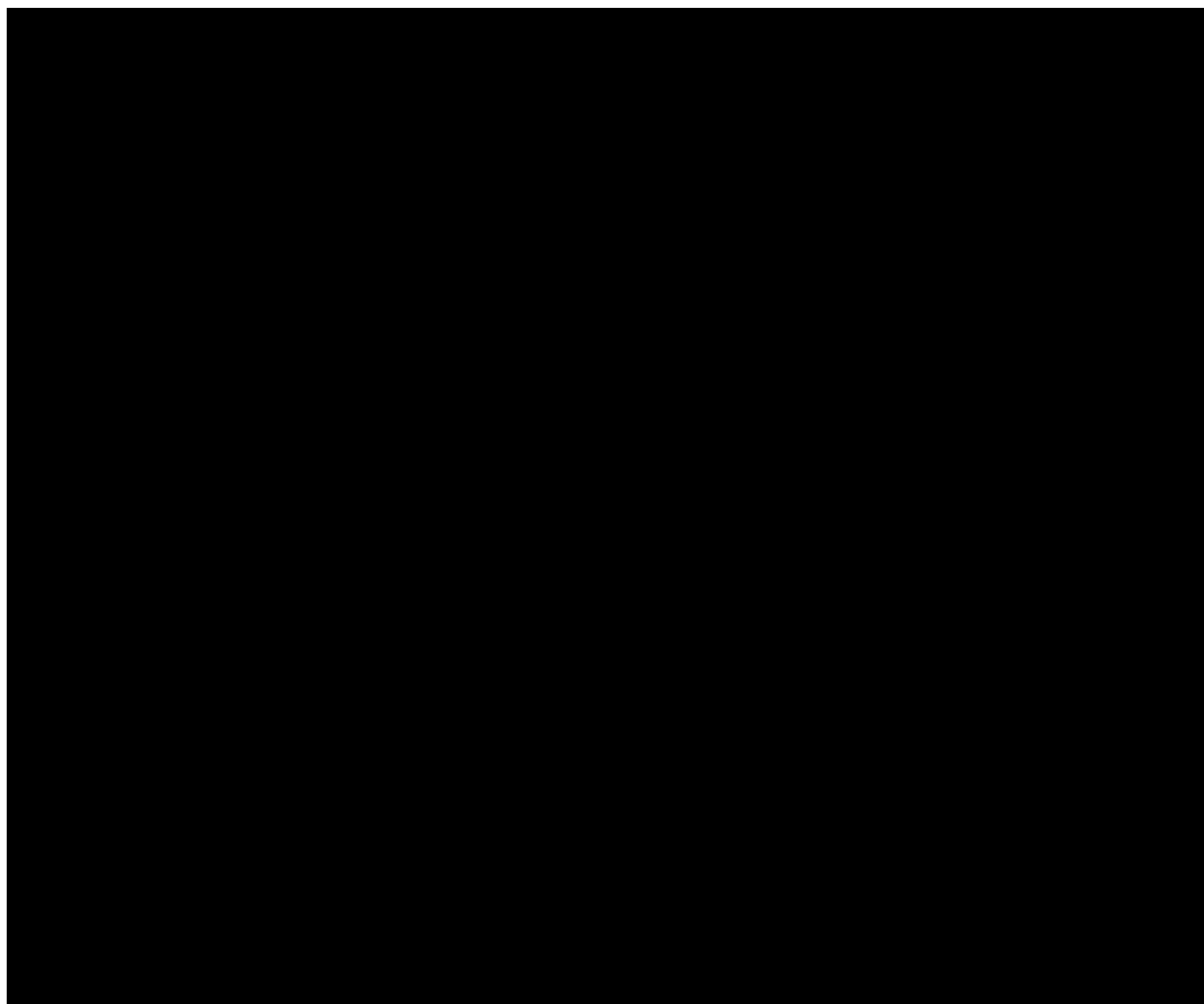
	Unadjusted Epcoritamab FL (n = 81)	Adjusted Epcoritamab (N _{eff} = 28)	HMRN (n = ■)
Age ≥ 60	69.1%	■	■
Male	65.4%	■	■
ECOG performance status 0 [†]	49.4%	■	■
Disease Stage III – IV [†]	85.2%	■	■
FLIPI Score 3,4,5 [†]	70.4%	■	■
Prior ASCT	18.5%	■	■
Prior CAR-T	7.4%	■	■
POD24 after first line CIT	37.0%	■	■
Refractory to most recent anti-lymphoma therapy	76.5%	■	■
Refractory to both anti-CD20 and an alkylator	74.1%	■	■
Prior lines of therapy ≥4	49.4%	■	■
Prior treatment with R ²	30.9%	■	■

[†] At baseline in EPCORE NHL-1, at diagnosis for HMRN.

ASCT, autologous stem cell transplant; CAR T, chimeric antigen receptor (CAR) T-cell therapy; CIT, chemoimmunotherapy; ECOG, Eastern Cooperative Oncology Group; FL, Follicular Lymphoma; FLIPI, Follicular Lymphoma International Prognostic Index; N_{eff}, effective sample size

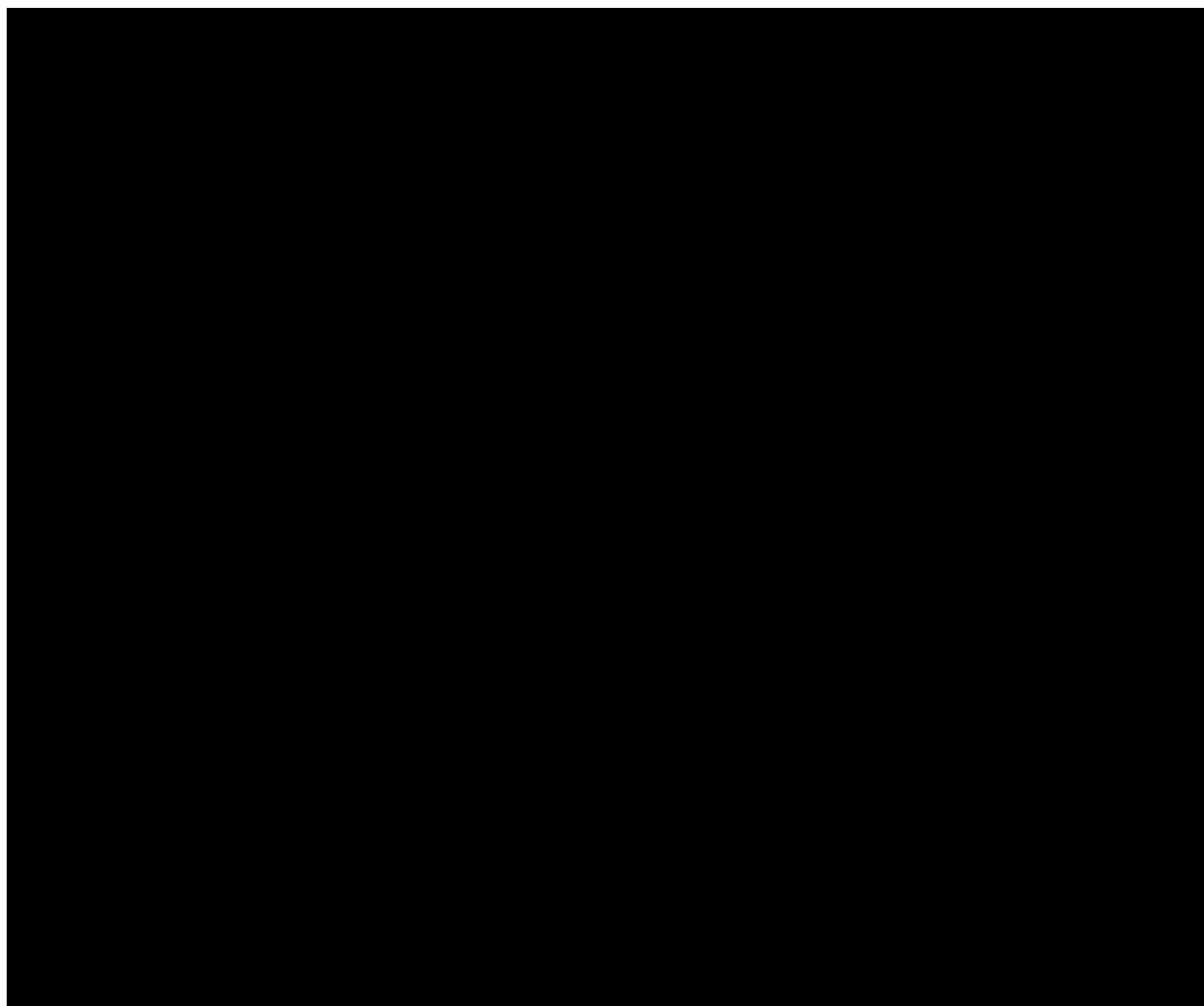
Kaplan–Meier curves for the MAIC-unadjusted and -adjusted epcoritamab data and comparator data are presented below for both OS and PFS (Figure 3 and Figure 4).

Figure 3. MAIC sensitivity analysis 1: Unadjusted and adjusted overall survival for EPCORE- NHL-1 vs HMRN in 4L+ indication



HMRN, Haematological Malignancy Research Network; MAIC, matching-adjusted indirect comparison; OS, overall survival

Figure 4. MAIC sensitivity analysis 1: Unadjusted and adjusted progression-free survival for EPCORE- NHL-1 vs HMRN in 4L+ indication



HMRN, Haematological Malignancy Research Network; MAIC, matching-adjusted indirect comparison; PFS, progression-free survival

The outcomes of this sensitivity analysis are presented in Table 5. The MAIC-adjusted OS was significantly better for epcoritamab compared with current 4L+ care (HR = [REDACTED], [REDACTED]) and is more favourable for epcoritamab compared with the base case analysis presented within the Company Submission. PFS was also significantly better for epcoritamab compared with current 4L+ care (HR = [REDACTED], [REDACTED]) and more favourable for epcoritamab compared with the base case.

Table 5. MAIC sensitivity analysis 1: Unadjusted and matched MAIC-adjusted OS and PFS for EPCORE NHL-1 vs current 4L+ care in 4L+ indication

OS	HR [95% CI]	p-value
Unadjusted		
Adjusted		
PFS	HR [95% CI]	p-value
Unadjusted		
Adjusted		

HR, hazard ratio; MAIC, matching-adjusted indirect comparison; PFS, progression free survival; OS, overall survival

This scenario analysis was performed to explore the impact of including ECOG and FLIPI score in the matching. As it could be argued that the outcomes of this sensitivity analysis are biased in favour of epcoritamab (by ECOG performance status and FLIPI score only being available at diagnosis in the HMRN data set), as well as the low effective sample size being likely to impact the precision of estimated outputs, AbbVie did not present this analysis in the Company Submission.

Sensitivity Analysis 2 – Patient refractoriness to prior therapies

In the second sensitivity analysis, AbbVie explored the impact of alternative refractory characteristics available from EPCORE NHL-1 and HMRN. This approach was undertaken to determine whether varying the definition for refractory status, an important prognostic factor identified by UK clinicians, would impact the outputs of the MAIC. Specifically, the ‘Refractory to most recent anti-lymphoma therapy’ and ‘Refractory to both anti-CD20 and an alkylator’ variables included in the base case analysis were replaced with the ‘Primary refractory’ and ‘Refractory to any prior anti-CD20 therapy’ variables. After match-adjusting the EPCORE population to HMRN, the effective sample size for epcoritamab patients is 31 (Table 6).

Table 6. MAIC sensitivity analysis 2: Baseline characteristics for epcoritamab vs HMRN in 4L+ indication

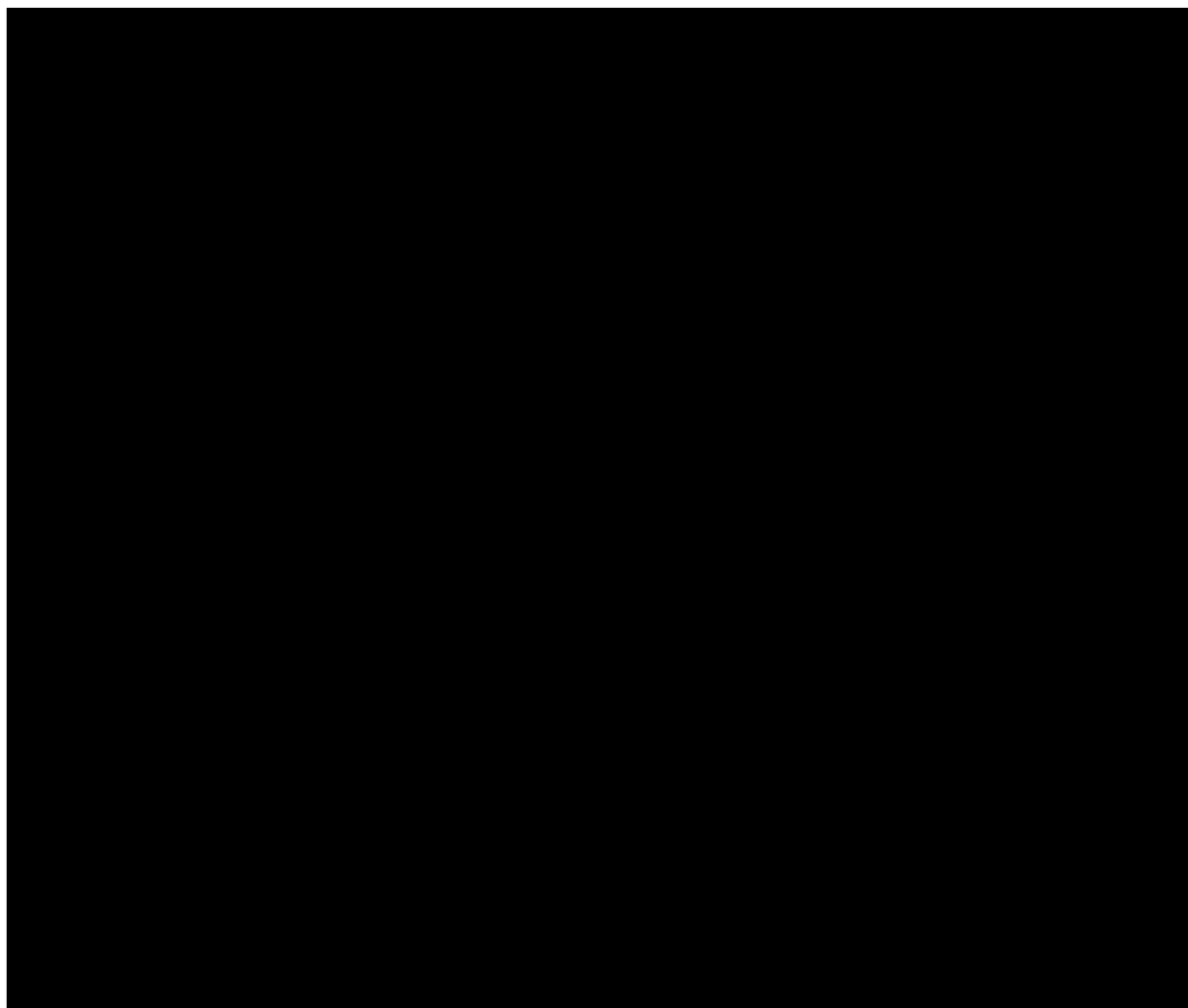
	Unadjusted Epcoritamab FL (n = 81)	Adjusted Epcoritamab (N _{eff} = 31)	HMRN (n = 1)
Age ≥ 60	69.1%	████	████
Male	65.4%	████	████
Disease Stage III – IV [†]	85.2%	████	████
Prior ASCT	18.5%	████	████
Prior CAR-T	7.4%	████	████
POD24 after first line CIT	37.0%	████	████
Primary refractory	50.6%	████	████
Refractory to any prior anti-CD20 therapy	82.7%	████	████
Prior lines of therapy ≥4	49.4%	████	████
Prior treatment with R ²	30.9%	████	████

[†] At baseline in EPCORE NHL-1, at diagnosis for HMRN.

ASCT, autologous stem cell transplant; CAR T, chimeric antigen receptor (CAR) T-cell therapy; CIT, chemoimmunotherapy; FL, Follicular Lymphoma; N_{eff}, effective sample size

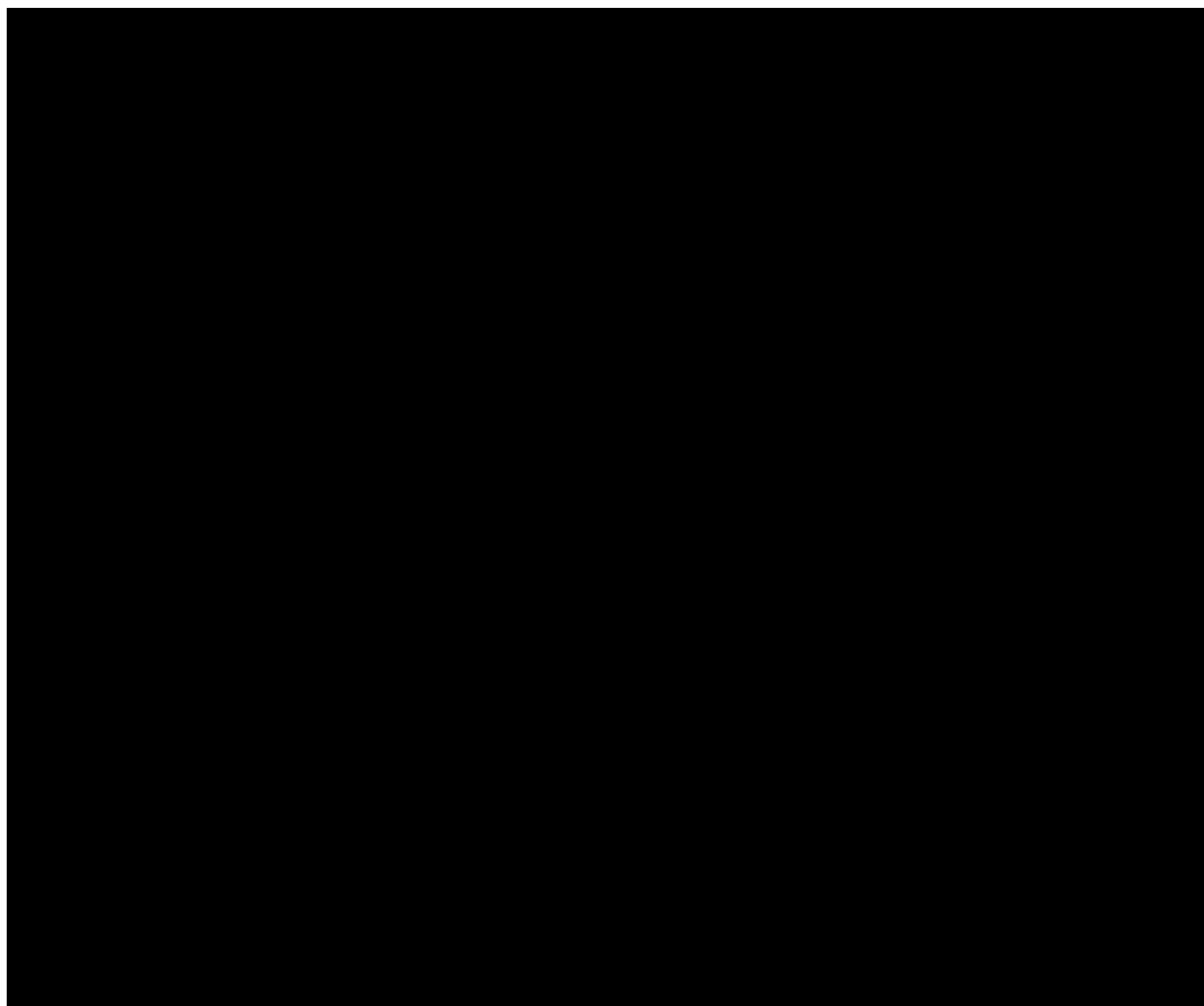
Kaplan–Meier curves for the MAIC-unadjusted and -adjusted epcoritamab data and comparator data are presented below for both OS and PFS (Figure 5 and Figure 6).

Figure 5. MAIC sensitivity analysis 2: Unadjusted and adjusted overall survival for EPCORE- NHL-1 vs HMRN in 4L+ indication



HMRN, Haematological Malignancy Research Network; MAIC, matching-adjusted indirect comparison; OS, overall survival

Figure 6. MAIC sensitivity analysis 2: Unadjusted and adjusted progression-free survival for EPCORE- NHL-1 vs HMRN in 4L+ indication



HMRN, Haematological Malignancy Research Network; MAIC, matching-adjusted indirect comparison; PFS, progression-free survival

The outcomes of this sensitivity analysis are presented in Table 7. The MAIC-adjusted OS was significantly better for epcoritamab compared with current 4L+ care (HR = [REDACTED], [REDACTED]) and is more favourable for epcoritamab compared with the base case analysis presented within the CS (Table 7). PFS was also significantly better for epcoritamab compared with current 4L+ care (HR = [REDACTED], [REDACTED]) and more favourable for epcoritamab compared with the base case.

Table 7. MAIC sensitivity analysis 2: Unadjusted and matched MAIC-adjusted OS and PFS for EPCORE NHL-1 vs current 4L+ care in 4L+ indication

OS	HR [95% CI]	p-value
Unadjusted		
Adjusted		
PFS	HR [95% CI]	p-value
Unadjusted		
Adjusted		

HR, hazard ratio; MAIC, matching-adjusted indirect comparison; PFS, progression free survival; OS, overall survival

This scenario analysis was performed to explore the impact varying the definitions of ‘refractory’ to explore how matching for different variables relating to a patients’ refractoriness to prior therapy impacts MAIC outputs. Although this sensitivity analysis yielded improved efficacy outcomes for epcoritamab compared with current 4L+ care, the effective sample size for this analysis was 31 patients, which is lower than the effective sample size used in the base case presented in the Company Submission and may lead to imprecise outputs. Therefore, AbbVie maintain that the variables selected and adjusted in its base case analysis are conservative and most appropriate.

Summary of Sensitivity Analyses

A summary of these sensitivity analyses is provided in Table 8 alongside the base case analysis presented in the Company Submission.

Table 8. Summary of MAIC sensitivity analyses

	Base case analysis	Sensitivity Analysis 1	Sensitivity Analysis 2
Variables adjusted for	Age ≥ 60 yrs Sex (male) Disease stage Prior ASCT Prior CAR-T POD24 of 1L CIT Refractory to last prior therapy	Age ≥ 60 yrs Sex (male) ECOG PS 0 Disease stage FLIPI score 3,4,5 Prior ASCT Prior CAR-T POD24 of 1L CIT	Age ≥ 60 yrs Sex (male) Disease stage Prior ASCT Prior CAR-T POD24 of 1L CIT Primary refractory

	Double refractory Prior lines ≥ 4 Prior R ²	Refractory to last prior therapy Double refractory Prior lines ≥ 4 Prior R ²	Refractory to any prior CD20 therapy Prior lines ≥ 4 Prior R ²
ESS	40	28	31
OS HR [95% CI]			
PFS HR [95% CI]			

ASCT, autologous stem cell transplant; CAR-T, chimeric antigen receptor therapy; CI, confidence interval; CIT, chemoimmunotherapy; ECOG, eastern cooperative oncology group; ESS, effective sample size; FLIPI, follicular lymphoma international prognostic index; HMRN, Haematological malignancy research network; HR, hazard ratio; OS, overall survival; PFS, progression free survival.

Variables in red font in the sensitivity analyses highlight differences in variable selection from the base case analysis.

Considering the sensitivity analyses performed above it can be seen that the MAIC is robust to alternative matching assumptions and reaffirms the approach taken in the base case. As reported in the Company Submission, variables of interest were identified through consultation with UK clinical experts, precedence from prior NICE TAs in FL and where there was a strong degree of evidence for association with survival outcomes.^{6,7} These scenarios show that the base case analysis was not biased in favour of epcoritamab and maintained a suitable effective sample size for decision making.

A25. Priority Question: Please rerun the MAIC ITC using the non-COVID modified cohort (i.e. with COVID-19 deaths included)

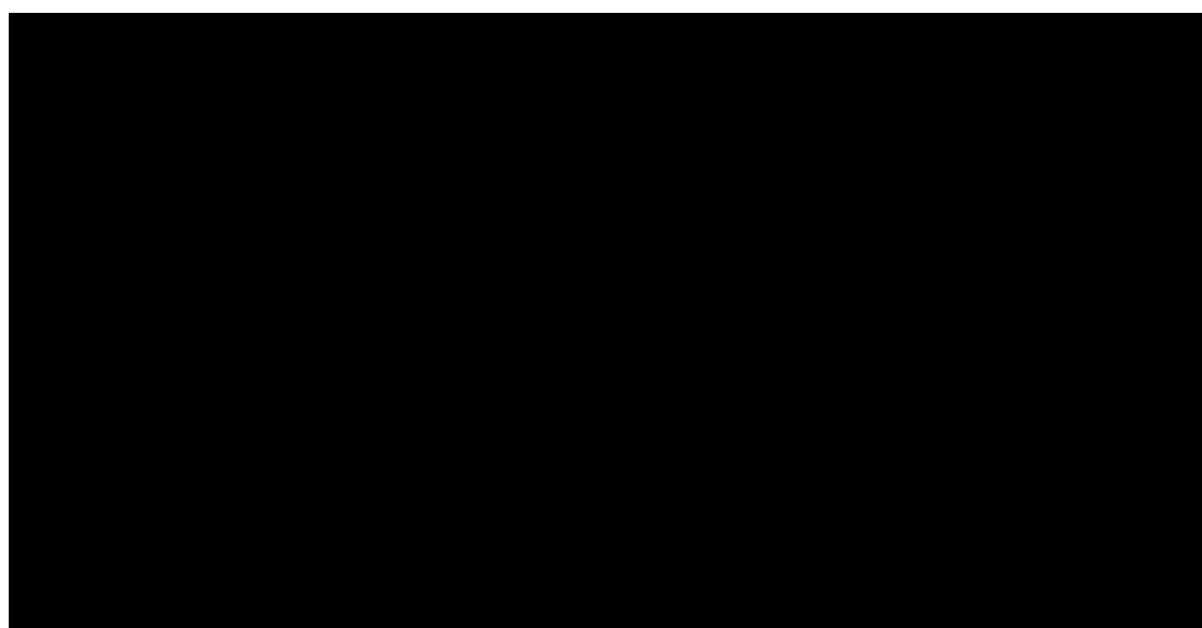
In the original submission, AbbVie presented an ITC using COVID-modified data from the EPCORE NHL-1 trial, where deaths attributed to COVID-19 were censored. Following the EAG's request, and to provide transparency to the Committee, a MAIC for the COVID-unmodified data from EPCORE NHL-1 has been conducted as per the methodology outlined in Section 2.12 of the Company Submission. The outcomes of this analysis on OS and PFS are presented in Table 9 and Figure 7. PFS remained significantly better for epcoritamab compared with current 4L+ care (adjusted HR = ). The adjusted OS also remained significantly better for epcoritamab compared with current 4L+ care (adjusted HR = ).

Table 9. Unadjusted and matched MAIC-adjusted OS and PFS of EPCORE NHL-1 COVID-modified and COVID-unmodified MAICs vs current 4L+ care in 4L+ indication

	COVID-modified		COVID-unmodified	
MAIC unadjusted				
Outcome	HR [95% CI]	p-value	HR [95% CI]	p-value
OS	██████████	██████	██████████	██████
PFS	██████████	██████	██████████	██████
MAIC Adjusted				
Outcome	HR [95% CI]	p-value	HR [95% CI]	p-value
OS	██████████	██████	██████████	██████
PFS	██████████	██████	██████████	██████

CI, confidence interval; HR, hazard ratio; MAIC, matching-adjusted indirect comparison; PFS, progression free survival; OS, overall survival

Figure 7. Unadjusted and adjusted OS and PFS for the EPCORE NHL-1 COVID-unmodified patient population vs HMRN in 4L+ indication



HMRN, Haematological Malignancy Research Network; MAIC, matching adjusted indirect comparison; OS, overall survival; PFS, progression free survival

Outcomes presented in Table 9 and Figure 7 reflect the mortality rate associated with COVID-19 at the height of the pandemic and as such, are not generalisable to UK practice. It is highly likely that patients would have continued to experience positive outcomes had it not been for the COVID-19 pandemic. As noted in response to Question A25, █ of the █ deaths attributed to COVID-19 occurred in patients who

were in CR at the time of their death. Additionally, patients who died due to COVID-19 presented with a better prognosis (■■■■% FLIPI 3-5) compared with patients who died due to other causes (■■■■% FLIPI 3-5). They also presented with risk factors that are highly predictive of death due to COVID-19, such as older age and high BMI (Appendix 1). As such, this cohort of patients were pre-disposed to COVID-19 related mortality when it is likely that they would have maintained their positive outcomes.

Scenario analysis: Censoring patients who died during the omicron wave of the COVID-19 pandemic

As noted in Section 2.6.2.1 in the Company Submission, the dose expansion cohort in the EPCORE NHL-1 trial had been adversely affected by the Omicron wave of the pandemic. Following the Omicron wave of the pandemic, a further ■ deaths could be attributed to COVID-19 in the dose expansion cohort. The dose optimisation part of the EPCORE NHL-1 trial (presented in Section 2.14 of the Company Submission) took place outside of the Omicron wave of the COVID-19 pandemic. No deaths were attributed to COVID-19 in the dose optimisation cohort. Accordingly, a scenario has been explored whereby COVID-related mortality during the Omicron wave of the pandemic had been censored, as this wave incurred higher mortality rates compared with the current variants of COVID-19. In this scenario analysis (Table 10), patients who died during the Omicron wave of the COVID-19 pandemic (defined as the period whereby Omicron had been a “Variant of Concern” for the World Health Organisation, from 26 November 2021 until 15 March 2023)^{8,9} were censored, resulting in ■ patients being censored for OS and ■ patients being censored for PFS. Table 10 compares the outputs of this Omicron-modified scenario (in which the ■ COVID-19 deaths during the Omicron wave were censored) with the outputs from the COVID-modified scenario in the company base case (in which all ■ COVID-19 deaths were censored).

The scenario analysis showed that epcoritamab reduces the risk of death by ■ compared with current 4L+ care (adjusted HR = ■). Treatment with epcoritamab also significantly reduced the risk of progression or death (PFS) by ■ compared with current 4L+ care (adjusted HR = ■). AbbVie maintains that the COVID-modified analysis

presented in the base case is the most applicable to current UK practice, with the Omicron-censored analysis being the next most applicable alternative. Both of these scenarios are likely to be more generalisable to current UK practice than the COVID-unmodified analysis due to the absence of risk associated with the Omicron wave.

Table 10. Unadjusted and matched MAIC-adjusted OS and PFS of EPCORE NHL-1 COVID-modified and Omicron-modified MAICs vs current 4L+ care in 4L+ indication

	COVID-modified		Omicron-modified	
MAIC unadjusted				
Outcome	HR [95% CI]	p-value	HR [95% CI]	p-value
OS				
PFS				
MAIC Adjusted				
Outcome	HR [95% CI]	p-value	HR [95% CI]	p-value
OS				
PFS				

CI, confidence interval; HR, hazard ratio; MAIC, matching-adjusted indirect comparison; PFS, progression free survival; OS, overall survival

Although the significantly improved outcomes for epcoritamab compared with current 4L+ care continue to be observed in the COVID-unmodified analysis, the inclusion of deaths attributed to COVID-19 results in outcomes that do not reflect current practice in the UK. The UK is no longer experiencing a high number of COVID-19 related deaths relative to the peak of the COVID-19 pandemic.¹⁰ Additionally, it is not expected that this will change in the future. Therefore, AbbVie maintain that the COVID-modified analysis is the most appropriate for decision making.

A26. Could the company clarify whether an STC was attempted and found infeasible, or ruled out a priori? If attempted and found infeasible, was any exploratory STC performed with a reduced set of prognostic variables to assess feasibility?

As outlined in the Company Submission, simulated treatment comparison (STC)-based parametric or semiparametric regression analyses rely on the number of events (not the number of patients) to determine the degrees of freedom; the lower the number of events, the lower the number of predictors that can be included in the

model. As such, an STC would not have been appropriate in this submission due to the small number of events recorded in the EPCORE NHL-1 study, which in turn would reduce the number of predictors that could be included in the model. In addition, MAICs are the preferred method of analysis when analysing time-to-event data for a single target comparator (or single RWE database) across multiple treatment outcomes, whereas STCs are more appropriate for analyses against multiple comparators.¹¹

Further, conducting an STC on time-to-event outcomes requires a parametric distribution (e.g. exponential, Weibull, etc.) of the best fit to be specified for the outcome, and an assessment performed regarding whether the same distribution is applicable to both arms of the analysis.¹² The choice of the parametric distribution in an STC is a critical assumption, and misspecification of the parametric distribution can lead to biased results. The choice of the parametric curve for the STC would introduce another layer of uncertainty next to the additional aspects of a correct specification of the outcome model and the assumption that the relationship between baseline covariates and the outcome is the same in both studies.

MAICs have routinely been presented to and accepted by NICE as valid methodology across various appraisals of lymphoma therapies. The MAIC in this submission was conducted utilising learnings from previous NICE TAs: TA627, TA892 and TA894.

Based on the rationale above, it was determined that a STC would not be an appropriate method for comparing epcoritamab with current 4L+ care and AbbVie did not perform such an analysis.

Survival Analysis

A27. Did the company explore flexible models such as piecewise or splines? If so, why were they not presented in the submission?

AbbVie did not consider flexible approaches to survival analyses to be appropriate for modelling efficacy outcomes in patients with 4L+ R/R FL who received epcoritamab. AbbVie notes that the standard parametric methods applied within the submission produce good visual and statistical fit to the observed data and long-term outcomes that are aligned with survival estimates aligned with clinical expectations,

as per our consultation with UK clinical experts experienced in treating patients with 4L+ FL; therefore, the use of more complex statistical models such as splines would add little additional value beyond the standard parametric models.

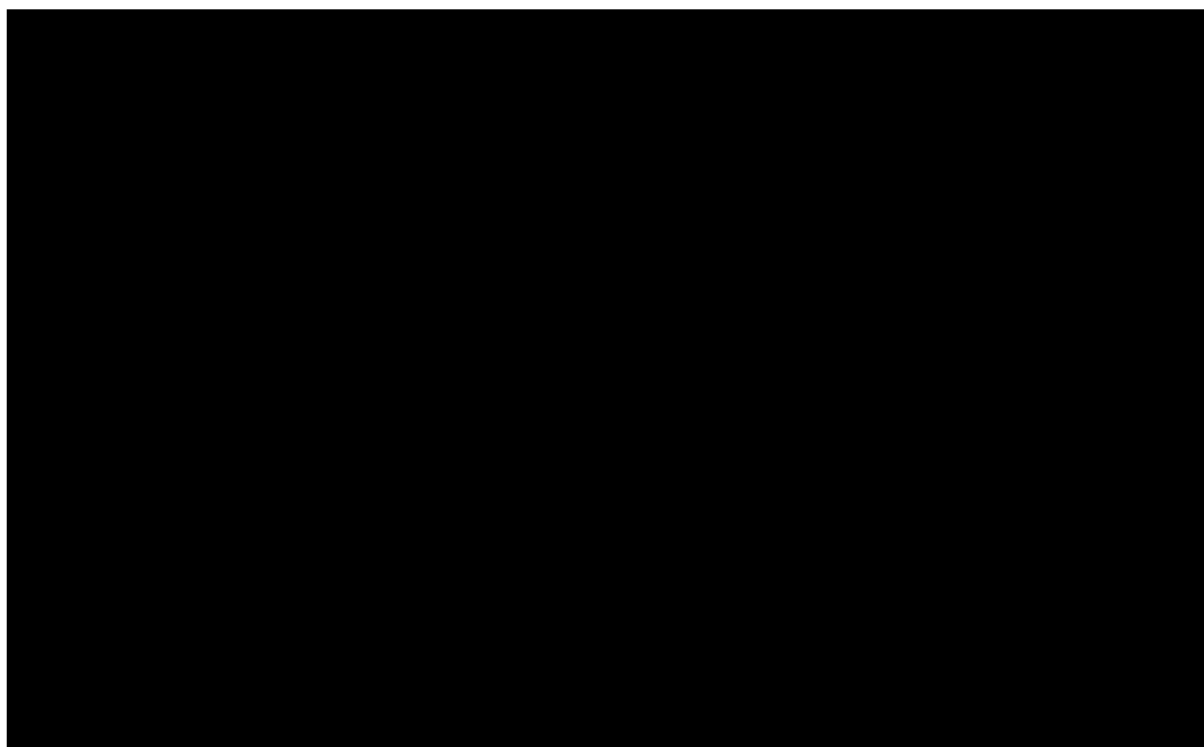
Implementing semi-parametric approaches (e.g. piecewise or spline-based models) to survival analysis involves subjective choices around the number and placement of cutpoints or knots, as well as the distribution applied to each segment. Further, these approaches to survival modelling risk overfitting to observed data and inherently assume that the data within each segment are sufficient for robust survival analysis. This assumption is likely to be particularly inappropriate in the tail of the Kaplan-Meier curve where fewer patients are at risk, causing individual events to become disproportionately impactful. As the outputs of flexible survival analyses can be sensitive to these assumptions and arbitrary decisions, implementing flexible survival modelling may lead to additional and unnecessary uncertainty, resulting in outputs that are clinically implausible and lack statistical robustness.

Overall, while AbbVie acknowledges the value of exploring more flexible approaches to survival analysis in cases where standard models do not fit the observed data well, this is not the case for epcoritamab. As described in Section 3.3.2 of the Company Submission, AbbVie made conscientious efforts to limit the uncertainty associated with the survival analyses by validating long-term estimates with clinicians experienced in treating patients with 4L+ FL; therefore, the company did not feel it was necessary to perform these analyses.

A28. Priority Question: Please provide the TTD KM plot for epcoritamab with the number at risk table, similar to Figure 27 in document B, without the survival models fitted.

The TTD KM plot for epcoritamab is provided in Figure 8. The median TTD is shown to have been reached shortly after ■ months. By ■ months of follow-up, almost all patients had discontinued from epcoritamab.

Figure 8. KM curve displaying epcoritamab TTD data



Cut-off date: [REDACTED], Median follow-up = [REDACTED] months, N=81

A29. Please fit survival models onto the HMRN curves, and then apply the HRs from the MAIC on those curves to estimate the efficacy of epcoritamab.

AbbVie have not provided this analysis as it would add additional, unnecessary uncertainty to the modelling. There are three primary reasons for this:

1. Only summary data is available from HMRN as opposed to individual patient data (IPD) being available from EPCORE NHL-1. As such, fitting survival models to the epcoritamab data where IPD were available and using the HRs from the MAIC to estimate outcomes for HMRN was deemed more appropriate, and allows for more accurate and precise estimation of survival.
2. The purpose of the MAIC is to align study populations and to estimate relative efficacy in these comparable populations. By then applying the hazard ratio to the epcoritamab survival curves means estimating HMRN efficacy in an EPCORE-NHL 1 population. This allows us to maintain consistency in the reference population for estimation of survival and other model inputs such as utilities, which are taken from EPCORE NHL-1.

3. The sample size in the HMRN dataset () is lower than the sample size from EPCORE NHL-1 (N = 81); therefore, it would be inappropriate to use the HMRN curves to fit survival models as this approach would likely lead to imprecise estimates of the efficacy of epcoritamab which would be unsuitable for decision making.

Producing the analyses in this way is aligned with precedent from previous NICE appraisals and means we can both estimate a relative effect in a comparable population whilst allowing us to retain the benefit of extrapolating from more robust IPD in a reference population that is aligned with other relevant model inputs. Extrapolating from HMRN and applying the inverse HR to generate outcomes from epcoritamab would disregard the availability and use of IPD and introduce unnecessary imprecision and uncertainty into the extrapolations.

A30. Priority Question: Why were the unadjusted epcoritamab curves used for survival models when the HRs applied are from the comparison of the MAIC-adjusted epcoritamab data versus HMRN?

The rationale here is similar to the rationale described in our response to A29 in that analyses have been conducted with the goal of minimising uncertainty and preserving consistency across the reference population used in the submission.

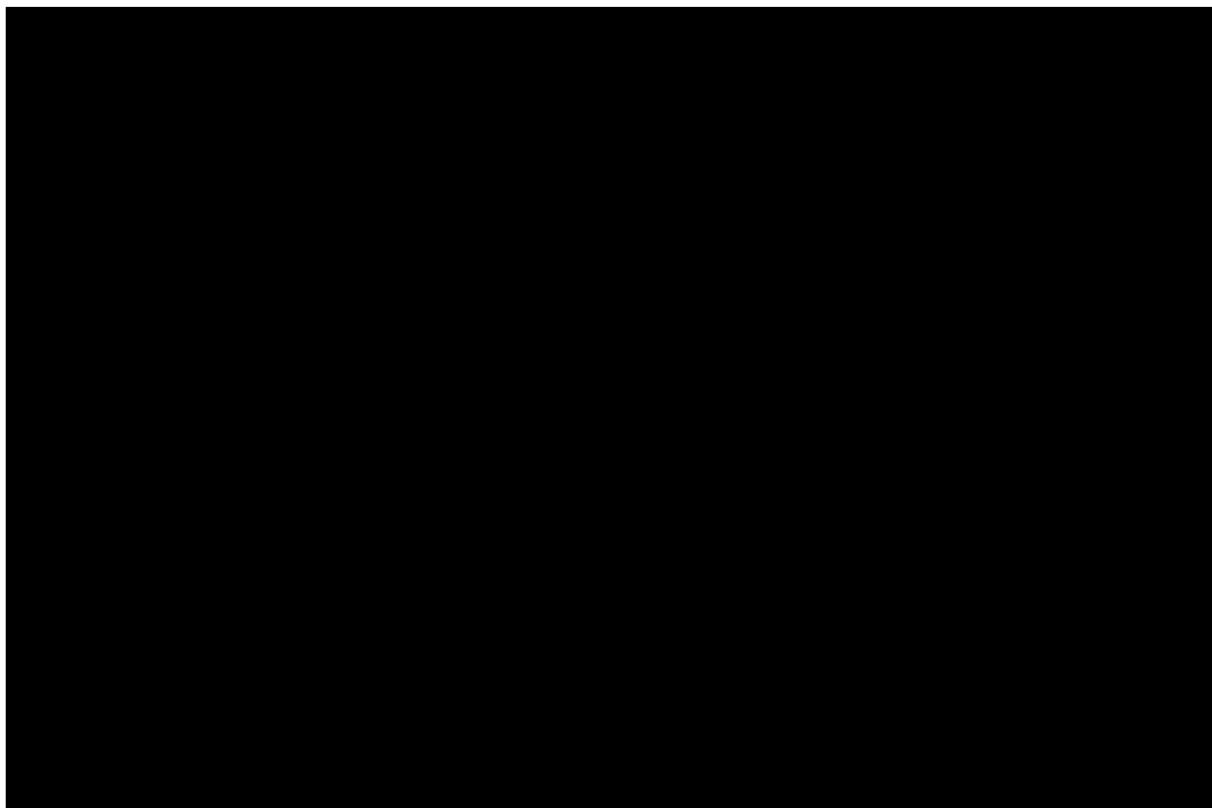
1. We have applied the HRs to the unadjusted epcoritamab survival data because the adjusted epcoritamab survival data produced as an output of the MAIC is inherently more uncertain given the impact of reduced effective sample size as a consequence of the matching.
2. To ensure that the estimation of survival considers an EPCORE NHL-1 reference population and to preserve alignment with other important model inputs it was deemed appropriate to apply the hazard ratios to the unadjusted data.

We acknowledge that a limitation of the MAIC is that it requires adjustment of the EPCORE NHL-1 population to a HMRN population before estimating relative effects. However, there is no reason to believe that this relative effect would not then hold in an EPCORE NHL-1 population and therefore, for the aforementioned reasons it was deemed appropriate to apply the hazard ratios to the unadjusted epcoritamab data.

A31. Please provide a figure similar to figure 33 in the CS document B of the parametric models fit on the current 4L+ care TTD data from HMRN over the trial length only.

This is provided in Figure 9 which displays the parametric models fit on the current 4L+ TTD data from HMRN observed over the trial length. As detailed in Table 56 of the Company Submission, the exponential distribution provides the best statistical fit to the observed data based on both AIC and BIC and is, therefore, applied in the base case analysis presented in the Company Submission.

Figure 9. Parametric distributions fit to the observed epcoritamab TTD data from EPCORE NHL-1



Cut-off date: [REDACTED], Median follow-up = [REDACTED] months, N=81

Section B: Clarification on cost-effectiveness data

B1. Can the company confirm the numbers in table 59 (PFS column, 'end of treatment' row) are correct.

AbbVie apologise for reporting errors in Table 59 of the Company Submission.
Please find the corrected numbers in the updated table below.

Table 11: Number of responses in the FL population of GCT3013-01 trial using the [REDACTED] DCO, by time point and health state

Time point	Numbers at risk*	Total observations	PFS	PD
Baseline:				
Day 1 Cycle 1	■	■	■	■
Day 1 Cycle 3	■	■	■	■
Day 1 Cycle 5	■	■	■	■
Day 1 Cycle 7	■	■	■	■
Day 1 Cycle 9	■	■	■	■
End of treatment	■	■	■	■

* Numbers of patients receiving treatment at Day 1 of cycle 1/3/5/7/9.
Abbreviations: PD, progressed disease; PFS, progression-free survival.

B2. Please can the company provide the rationale for excluding the costs of prophylactic corticosteroids, antihistamines and antipyretics that were given to patients in the expansion cohort iNHL FL 1-3A (n=81)

AbbVie has provided an updated version of the economic model including the functionality to include the costs of prophylactic corticosteroids, antihistamines and antipyretics in cycle 1 of epcoritamab dosing (cell G56 of the Main Board sheet).

The usage of concomitant medications is applied as per the optimisation part of EPCORE NHL-1, which aligns with anticipated dosing in the marketing authorisation. The costs associated with the use of these concomitant medications are applied each week for the first cycle of epcoritamab dosing (Table 12).

Table 12. Concomitant medications captured within the company model

	Corticosteroid	Antihistamine	Antipyretic
Therapy	Dexamethasone	Chlorphenamine	Paracetamol (acetaminophen)
Dosage	16 mg dexamethasone administered orally on days 1-4, days 8-11,	16 mg administered daily in cycle 1	1000 mg administered on days 1, 8, 15 and 22 of cycle 1

	days 15-18 and days 22-25 of cycle 1		
Price¹³	£35.97 Dexamethasone 4 mg soluble tablets / Pack size 50	£0.43 Chlorphenamine 4 mg tablets / Pack size 28	£0.79 Paracetamol 500 mg tablets / Pack size 100 -

The impact on results is presented in Table 13.

Table 13. Scenario analysis: Including concomitant medications

		Total			Incremental			
		Costs	LYs	QALYs	Costs	LYs	QALYs	ICER (£/QALY)
Base case	Epcoritamab	■	8.758	5.176	-	-	-	-
	Current 4L+ Care	■	1.740	1.182	■	7.018	3.994	■
Concomitant medications	Epcoritamab	■	8.758	5.176	-	-	-	-
	Current 4L+ Care	■	1.740	1.182	■	7.018	3.994	■

Analysis performed using epcoritamab PAS price

Costs and QALYs discounted; LYs undiscounted

Severity modifier of ×1.2 applied

ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years

As can be seen in Table 13, including concomitant medications during epcoritamab priming has a minor effect on total costs (increase of £■) and a negligible impact on the ICER (increase of £■/QALY). Therefore, the model is insensitive to the inclusion/exclusion of concomitant medications.

B3. Priority Question: Please can the company provide the rationale for differences in vial sharing assumptions in the model. Vial sharing allowed in the Epcoritamab arm and not allowed in the Current 4L+ care arm.

For therapies where body surface area (BSA) is used to determine dosage (rituximab and bendamustine) in the current 4L+ care arm, the dose administered to a patient is more individualised compared with a fixed dose regimen. As such, this analysis considers that concerted efforts for vial sharing could not reasonably be expected in clinical practice for these regimens; therefore, drug wastage was considered by assuming that patients receive only whole vials. In contrast, treatment with epcoritamab is performed using a fixed dose regimen; therefore, it is conceivable that efforts to minimise wastage when preparing the priming doses

might be performed. Nonetheless, AbbVie note that the option to include/exclude vial sharing for epcoritamab is provided in the economic model (Costs sheet, cells L45:L48) and have provided a scenario analysis in Table 14 below, where no vial sharing is assumed for either epcoritamab or current 4L+ care.

Table 14. Scenario analysis: No vial sharing for epcoritamab or current 4L+ care

		Total			Incremental			
		Costs	LYs	QALYs	Costs	LYs	QALYs	ICER (£/QALY)
Base case	Epcoritamab	██████	8.758	5.176	-	-	-	-
	Current 4L+ Care	██████	1.740	1.182	██████	7.018	3.994	██████
No vial sharing	Epcoritamab	██████	8.758	5.176	-	-	-	-
	Current 4L+ Care	██████	1.740	1.182	██████	7.018	3.994	██████

Analysis performed using epcoritamab PAS price

Costs and QALYs discounted; LYs undiscounted

Severity modifier of ×1.2 applied

ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years

As can be seen, and consistent with vial sharing only being relevant during epcoritamab priming, there is a minimal impact to the ICER compared with the base case (£██████), indicating that cost-effectiveness outcomes are not sensitive to this assumption.

B4. Priority Question: Please can the company provide information on the covariates used in the linear mixed model to estimate utilities from the EPCORE NHL-1 data and the regression model output.

Section 3.4.4.1 of the Company Submission highlights that engagements with clinical experts suggest that patients achieving CR are likely to experience a higher health-related quality of life (HRQoL) than those who do not achieve CR. Consequently, a Linear Mixed Model (LMM) analysis was conducted on a subset of patients in a progression-free health state. This analysis explored the covariate "CR status" (comparing patients who achieved CR at least once to those who did not) to inform the utilities used in the base-case analysis. The results of the regression model for this analysis are detailed in Table 64 of the Company Submission.

B5. Can the company confirm that no scenario analysis was performed to assess the impact on cost-effectiveness of costing the 'basket of 4L+ care' using the actual proportions reported in HMRN dataset?

AbbVie can confirm that this scenario analysis was not performed as it would rely on 19 different treatment regimens being included within the economic model, nine of which were received by single patients. As such, an analysis fully exploring the proportions reported in the HMRN dataset would introduce superfluous complexity in drug costs and be overly reliant on individualised treatment regimens. In its base case, AbbVie grouped each therapy into four classes and costed these according to the most frequently used treatment option in clinical practice and, therefore, the therapies that epcoritamab is most likely to displace. AbbVie maintains that this approach remains pragmatic and most appropriate.

B6. Priority Question. Can the company justify not exploring alternative AE proportions in the comparator arm that account for the varying proportions of AEs occurring across different treatment regimens e.g. OB-bendamustine and R² as reported in TA627 (company cites TA894)

As detailed in the Company Submission, the limited available data reporting AE outcomes for chemotherapy hinders the ability to model safety outcomes using a basket approach. Therefore, since R-Chemo was the second largest sub-basket in current 4L+ care, data for R-CHOP was used in the analysis. This approach is mindful of the paucity of data for the target patient population and aims to reflect the treatment landscape for 4L+ FL as appropriately as possible.

In response to the EAG's question, AbbVie has performed additional scenarios using the AE proportions presented in TA627 and TA894.

Table 15. Adverse event proportions presented in TA627 and TA894 applied for additional scenario analyses

Adverse event	O-Benda GADOLIN (n = 204)	R-CVP RELEVANCE (n = NR)	R ² MAGNIFY (n = 128)
Neutropenia	27.50%	85.30%	42.20%
Anaemia	5.40%	4.50%	3.10%
Leukopenia	0.00%	16.60%	7.00%
Lymphopenia	0.00%	0.00%	3.10%

Thrombocytopenia	10.30%	0.00%	5.50%

NR, not reported

† For R², patients who experienced a decreased white blood cell count (3.90%) were assumed to be captured within the proportion of patients experiencing leukopenia (7.00%) and are therefore not considered separately to avoid double counting.

The impact of varying these adverse event proportions is presented in Table 16.

Table 16. Scenario analysis: Varying AE proportions

		Total			Incremental			
		Costs	LYs	QALYs	Costs	LYs	QALYs	ICER (£/QALY)
Base case	Epcoritamab	██████	8.758	5.176	-	-	-	-
	Current 4L+ Care	██████	1.740	1.182	██████	7.018	3.994	██████
O-Benda	Epcoritamab	██████	8.758	5.176	-	-	-	-
	Current 4L+ Care	██████	1.740	1.182	██████	7.018	3.994	██████
R-CVP	Epcoritamab	██████	8.758	5.176	-	-	-	-
	Current 4L+ Care	██████	1.740	1.182	██████	7.018	3.994	██████
R ²	Epcoritamab	██████	8.758	5.176	-	-	-	-
	Current 4L+ Care	██████	1.740	1.182	██████	7.018	3.994	██████

Analysis performed using epcoritamab PAS price

Costs and QALYs discounted; LYs undiscounted

Severity modifier of ×1.2 applied

ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years

As can be seen in Table 16, varying the proportion of adverse events for the current 4L+ care arm using available data sources has a limited impact on the ICER outputs, indicating that cost-effectiveness outcomes are not sensitive to these inputs.

B7. Can the company confirm that the costs of disease progression in the model were applied only to the patients that progressed to the PD state.

AbbVie can confirm that the costs of disease progression were only applied to patients who progressed to the PD state. The calculations for this are in two separate sheets in the model. Firstly, in the Costs & Effects total sheet, cells P7 and P8 calculate the undiscounted costs for both the intervention and the comparator, whilst cells P14 and P15 calculate the discounted costs. The formula in cells P14 and P15 finds the difference between the number of patients with progressed disease in the current cycle and those in the previous cycle. To account for mortality, it then adds the change in deaths between the two cycles. The change in deaths is

added because any patient who progresses to PD and then dies in the same cycle would never contribute to a net rise in the PD count. By adding deaths back in, it captures those who transition from PD to death and avoids underestimating how many actually entered the PD state. If applicable, these formulas are then multiplied by the discount factor.

In order to ensure that this calculation is correct. A second calculation is added to the Trace_EPCO sheet, where in column AP this calculation is replicated for every cycle and then summed in cells AP14 and AP15. The totals in these cells are identical to those found in the Costs & Effects total sheet, providing reassurance that the calculations have been completed correctly.

Section C: Textual clarification and additional points

C1. CS Section 2.7 states ‘A full quality assessment of the trial using the Down’s and Black checklist is provided in the data extraction file, included in the Clinical SLR report in Appendix B’. Please provide this.

Please find the requested Down’s and Black checklist in Table 17.

Table 17. Down’s and Black checklist for EPCORE NHL-1

Title	EPCORE NHL-1
Reporting	
1. Is the hypothesis/aim/objective of the study clearly described?	Yes
2. Are the main outcomes to be measured clearly described in the Introduction or Methods section?	Yes
3. Are the characteristics of the patients included in the study	Yes
4. Are the interventions of interest clearly described?	Yes
5. Are the distributions of principal confounders in each group of subjects to be compared clearly described?	N/A
6. Are the main findings of the study clearly described?	Yes
7. Does the study provide estimates of the random variability in the data for the main outcomes?	Yes
8. Have all important adverse events that may be a consequence of the intervention been reported?	Yes
9. Have the characteristics of patients lost to follow-up been described?	No
10. Have actual probability values been reported (e.g., 0.035 rather than <0.05) the main outcomes except where the probability value is less than 0.001?	No
External validity	

11. Were the subjects asked to participate in the study representative of the entire population from which they were recruited?	Unsure
12. Were those subjects who were prepared to participate representative of the entire population from which they were recruited?	Unsure
13. Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?	Unsure
Internal validity - bias	
14. Was an attempt made to blind study subjects to the intervention they have received?	No
15. Was an attempt made to blind those measuring the main outcomes of the intervention?	No
16. If any of the results of the study were based on "data dredging", was this made clear?	Unsure
17. In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?	No
18. Were the statistical tests used to assess the main outcomes?	Yes
19. Was compliance with the intervention/s reliable?	Unsure
20. Were the main outcome measures used accurate (valid and reliable)?	Yes
Internal validity - confounding	
21. Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?	N/A
22. Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?	N/A
23. Were study subjects randomised to intervention groups?	N/A
24. Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?	N/A
25. Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?	Yes
26. Were losses of patients to follow-up taken into account?	Unsure
Power	
27. Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?	Yes

C2. How many reviewers were involved in screening of full papers in the SLR?

All full-text publications were screened independently by two reviewers using the DistillerSR platform. A third reviewer was consulted and adjudicated if the two reviewers did not reach agreement on eligibility of individual full-text publications.

C3. Appendix Table 13: Patients receiving second or later lines of therapy were initially included in the SLR.

- a. How many reviewers were involved in the step of excluding studies of patients receiving second line?*

Exclusion of publications that reported only 2L+ data was conducted in the same manner as the screening of titles/abstracts and full-text publications. Two reviewers independently assessed the availability of data by treatment line within the publications. A third reviewer was consulted and adjudicated if the two reviewers did not reach agreement on eligibility of individual full-text publications.

- b. Were full papers of all 238 excluded studies checked to see if any relevant subgroup data at 3L+ were reported?*

AbbVie can confirm that the full-text publications of the 238 excluded publications (including any available supplementary material) were checked to ensure that no relevant 3L+ data were reported. This check was done for all 345 publications that progressed to inclusion (see PRISMA in Figure 3 of the Company Submission). Of the 107 publications that ultimately progressed to extraction, several were in a 2L+ population but reported relevant 3L+ data.

- c. Please provide reference details of the 238 excluded studies.*

Please see the reference pack for the reference information of the 238 excluded publications. AbbVie wish to reiterate that the clinical SLR was conducted from a global perspective and therefore captures information for a wider population than the target population of this submission (patients with 4L+ R/R FL).

C4. Appendix B.7 lists the excluded studies by authors, year and title. Please provide the full citations for the studies listed.

Please see the reference pack for the reference information of the full-text exclusions.

C5. Appendix B.2 states 107 publications reporting on 54 studies were included for data extraction. Of these 107 publications, 80 publications reporting on 38 studies presented 3L+ data only, the remaining 27 publications reporting on 17 studies

reported on both 3L+ and 4L+. The number of studies (38+17) totals 55, not 54. Please clarify.

AbbVie apologise for an error in the reporting of outcomes from the SLR. Some of the numbers provided in the submission were not correct and AbbVie agree that the description of the study numbers was not as clear as it could have been. The text should read: “107 publications reporting on 54 studies were included for data extraction. Of these 107 publications, 78 publications presented 3L+ data only, the remaining 29 publications presented on both 3L+ and 4L+. In total, 3L+ only data was available for 33 studies, and both 3L+ and 4L+ data were available for the remaining 21 studies”.

C6. In addition, B.4 Table 19 lists 19 studies presenting 4L+ treatment data. Please clarify how this relates to the 17 studies reporting on both 3L+ and 4L+ as stated in B.2 and Appendix Figure 1.

As with the response to Question C5, some of the numbers presented in Table 19 were not accurately presented in the Company Submission. The total number of studies presenting 4L+ data was 21, as described in Table 18.

Table 18. Outcomes captured in studies presenting 4L+ treatment data

Source	OS	PFS	EFS	DFS	TTNT	ORR	CR	PR	MRD	DoR	DoCR	TTR	TTCR	Cure rate
Avilés 2001	✓	✓				✓	✓	✓						
Bethge 2010	✓		✓				✓	✓						
BGB-3111-AU-003						✓								
Bremer 2003							✓	✓						
Budde 2022_phase II						✓	✓							
CITADEL-203						✓								
Coiffier 2011		✓												
DAWN						✓								
ELARA		✓				✓	✓							
ELM-2						✓								
GADOLIN		✓												
Metzner 2021	✓	✓												
ROSEWOOD						✓								
Sabloff 2007	✓	✓												
Salles 2020	✓					✓				✓				

SCHOLAR-5	✓	✓			✓	✓	✓							
Shah 2023					✓									
Unity-NHL						✓								
ZUMA-5	✓	✓			✓	✓	✓	✓	✓					
EPCORE NHL-1						✓	✓							
TRANSCEND FL	✓	✓				✓	✓	✓						

All 4L+ data is available in the data extraction file.

CR: complete response; DoCR: duration of complete response; DoR: duration of response; DFS: disease-free survival; EFS: event-free survival; MDR: minimal residual disease; ORR: overall response rate; OS: overall survival; PFS: progression-free survival; PR: partial response; TTCR: time to complete response; TTNT: time to next treatment; TTR: time to response

C7. For clarity, please provide a list of the included 54 (or 55) studies, indicating the primary publication and associated included publications, the lines of therapy reported (3L+, 4L+, both), and the intervention(s). Please indicate which of these studies are discussed in the review.

The correct number of studies is 54, all of which are discussed in the review. Please see the reference pack for the requested table.

C8. For all systematic literature reviews (SLRs), reported in Appendices B, E, F and G, please provide details of the electronic database search strategies, including numbers of results, from the original (March/April 2023) and first update (February/March 2024) searches.

The search strategies for the clinical and economic SLR searches (original and updates) are included in the reference pack.

C9. For the SLRs reported in Appendices B, E, F and G, please describe how duplicates were removed from the search results, both across different search updates and between different databases within the same search update or iteration.

Searches conducted in ProQuest across the EconLit, Embase and MEDLINE databases were run in parallel. ProQuest automatically removes duplicates between these databases from the exported search results. All exported references from ProQuest were imported into EndNote databases for each SLR. For the clinical SLR, search results from the Cochrane databases were downloaded and combined into the EndNote database. A further deduplication step was then performed within the EndNote database using the find duplicates feature.

Duplicates across updates were identified by comparing the list of included publications after screening with those from the previous iterations. Any duplicates at this stage were flagged and excluded for the reason of duplicate.

C10. Please explain how it is possible to have -1 results in Appendix F.1.5, Table 40, line S65, and then 54 results when this is limited by publication date in line S66.

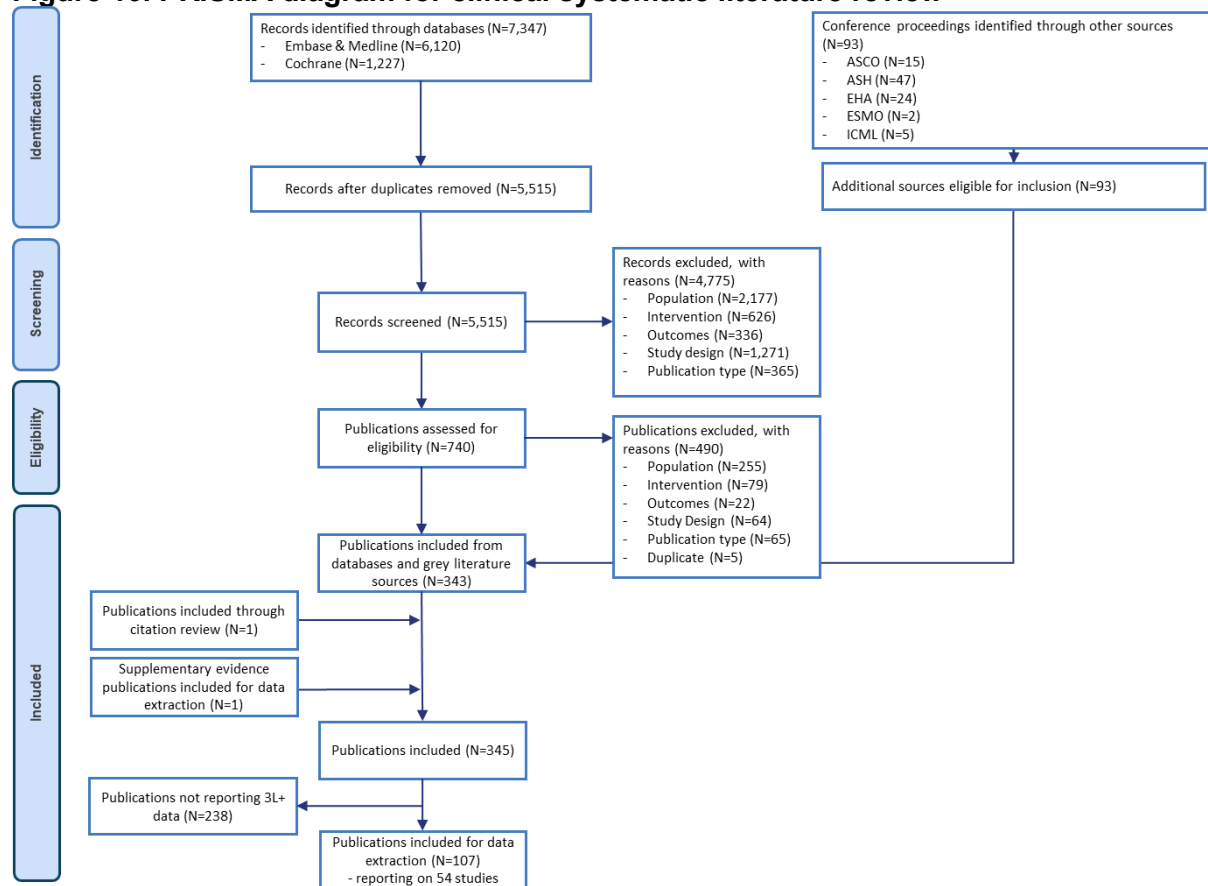
This “-1” value is due to an artifact in the ProQuest search platform. It is a known issue that occurs when the results of the individual search line have not had time to load. ProQuest will often display the results of the last search line (in this case line

S66) before the earlier search lines. When the search strategy is saved as an RTF file directly from ProQuest, any line that has not had time to load displays as “-1”. In this instance, it was an oversight as the RTF file was downloaded too early and hence this “-1” result displayed for line S65. Please note that this has no impact on the results of the final search line S66.

C11. In the PRISMA diagram and related text for the clinical effectiveness SLR (Appendix B.2 Figure 1), the numbers of reports assessed for eligibility at full-text screening is reported as 740. However, 5,515 records screened minus 4,755 excluded should leave 760, not 740 as reported. Please explain what happened to the additional 20 records.

Apologies, the number of full text exclusions in the PRISMA diagram should read 4,775 which matches the tally from the individual exclusion reasons that are presented. An updated version of the PRISMA diagram is presented in Figure 10.

Figure 10. PRISMA diagram for clinical systematic literature review



ASCO, American Society of Clinical Oncology; ASH, American Society of Hematology; EHA, European Hematology Society; ESMO, European Society for Medical Oncology; ICML, International Conference on Malignant Lymphoma

C12. In the PRISMA diagram for the clinical effectiveness SLR (Appendix B.2 Figure 1), one included publication is described as “Supplementary evidence publications included for data extraction”. Please explain what this means and how this publication was identified.

AbbVie identified multiple chart reviews in this SLR that did not match our PICOS, specifically because these studies often do not report outcomes per specific treatment but rather per drug class.

C13. For the clinical SLR, trials registers were searched in order to check that no relevant unpublished or ongoing trials had been missed by the electronic database searches, but these records were not included in the full SLR process (Appendix B.1.2, page 7). Please confirm whether any additional, relevant trials were found via

the trials register searches and if so, provide details of the trials and what was done with the data.

AbbVie can confirm that there were no additional relevant trials identified from this search that had not already been screened as part of the SLR.

References

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12. Macabeo B, Quenéchdu A, Aballéa S, et al. Methods for Indirect Treatment Comparison: Results from a Systematic Literature Review. *J Mark Access Health Policy*. 2024;12(2):58-80.
13. GOV.UK. Drugs and pharmaceutical electronic market information tool (eMIT). 2024.

Appendix 1

Table 19: Patient Baseline Demographic and Disease Characteristics – Patients with COVID-related and All Other Mortality in the Dose Expansion Cohort

	Expansion Part	
	COVID-Related Mortality (N = ■)	All Other Mortality (N = ■)
Age at informed consent (years)		
Mean (SD)	■■■■	■■■■
Median	■	■
Min, Max	■■■	■■■
Sex (at birth)		
Male	■■■■	■■■■
Female	■■■■	■■■■
Race		
White	■■■■	■■■■
Black or African American	■	■
Asian	■■■■	■
Other	■	■
Not reported	■■■■	■■■■
BMI (kg/m²) category at baseline		
<18.5	■	■
18.5 ≤ 25.0	■■■■	■■■■
25 ≤ 30	■■■■	■■■■
≥ 30.0	■■■■	■■■■
ECOG Performance status		
0	■■■■	■■■■
1	■■■■	■■■■
2	■■■■	■■■■
Baseline renal function classification by Cockcroft- Gault method (CrCl)[mL/min]		
Normal (≥ 90)	■■■■	■■■■
Mildly impaired (60≤ 90)	■■■■	■■■■
Moderately impaired (30 ≤ 60)	■■■■	■■■■
Severe impairment	■	■
Baseline hepatic function per NCI criteria		
Normal	■■■■	■■■■
Mild Dysfunction	■■■■	■■■■
Moderate dysfunction	■	■

Severe dysfunction	I	I
Disease type at trial entry		
FL Grade 1-3A	■	■
Histological grade		
1	■	■
2	■	■
3A	■	■
Not applicable	I	I
Median time for initial diagnose to first dose ^a (years)	■	■
FLIPI		
0-1	■	■
2	■	■
≥3	■	■
Unknown	I	I
Not applicable	I	I
Number of Prior Lines of Therapy		
Median	■	■
1	I	I
2	I	I
3	■	■
≥4	■	■
POD24		
Progression, transformation or relapse within 24 months of initiating first-line immunochemotherapy	■	■
Double refractory to anti-CD20 and alkylating agents, regardless of two treatments being in the same or different treatment lines	■	■
Bone Marrow Involvement		
Bone marrow involvement at baseline by investigator	■	■

Data cut ■■■■■, assessed by independent review committee

a. Time from diagnosis of disease recorded at time of study entry.

BMI, body mass index; CrCl, creatinine clearance; ECOG, Eastern cooperative oncology group; FL, follicular lymphoma; FLIPI, follicular lymphoma international prognostic index; NCI, National Cancer Institute; POD24, progression of disease 24 months; SD, standard deviation

Single Technology Appraisal
**Epcoritamab for treating relapsed or refractory follicular lymphoma after 2 or more
systemic treatments [ID6338]**

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1. Your name	[REDACTED]
2. Name of organisation	Follicular Lymphoma Foundation
3. Job title or position	[REDACTED]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Our mission is finding a cure for follicular lymphoma (FL) and fast. We are committed to finding a cure for FL by placing patients at the heart of everything we do, driving research, education, and impactful outcomes. The FLF is funded by industry sponsors, high-net-worth individuals, foundations and trusts and individual giving. We are not a member organisation.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] If so, please state the name of the company,	We have received the following funding from AbbVie: AbbVie – \$15,000 • FL Biomarker Discovery Program Genmab/AbbVie – \$76,000 • Uniting Experts, Patients, and Innovation in Follicular Lymphoma, to seek a Cure in an Integrated Program • Pioneering the Future of Immuno-Oncology in Follicular Lymphoma • Webinar Series 1 All of the above have had no influence on, control of, nor input into the development or performance of the programmes.

Patient organisation submission

Epcoritamab for treating relapsed or refractory follicular lymphoma after 2 or more systemic treatments [ID6338]

amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	As a patient organisation, we are in regular contact with a large and engaged FL community. Our recent insights are drawn from a diverse range of sources, ensuring we capture a broad spectrum of patient (and carer) experiences. We engage with independent patient groups of over 26,000 members and have a direct reach of over 15,000. Specifically, our main patient insights stem from data collected in the following ways: • Treatment preferences patient survey (168 global respondents) and round table/focus group discussion, Sept 2024. • Immunotherapy patient survey (791 global respondents) and round table/focus group discussion, June 2024 • Biomarker patient survey (714 global respondents) and round table/focus group discussion, November 2023 • Patient polls - Aug 2023, Sept 2021 • Regular feedback and information gathered through live webinar polls, Q+As and feedback surveys • Regular engagement in the independent patient groups

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Living with FL is often described by patients as living with a constant sense of uncertainty and unpredictability. Our patient insights have shown a wide range of experiences, from those on watch and wait with minimal symptoms to others undergoing their sixth line of treatment. The most common fear is that FL will return or transform into a more aggressive form. Fewer patients worry about rapid progression or treatment side effects, but many express concern about running out of treatment options and affording care. Our surveys have revealed that nearly half of patients find coping with uncertainty about the future to be the hardest challenge. Other major difficulties include balancing emotional wellbeing with physical symptoms, and feeling isolated or misunderstood. Constant anxiety, worrying that every new symptom is FL-related, is a common theme. Carers often share these emotional burdens. We hear that carers play a crucial role in daily life and treatment, and they too struggle with anxiety, helplessness, and the need for their own support.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	The current treatments available for R/R FL patients are very limited, unless they transform to DLBCL, where CAR-T is already approved. Our patient insights have shown that in general people are aware that innovative treatments exist but there are major knowledge gaps and concerns around accessibility.
8. Is there an unmet need for patients with this condition?	There is a clear unmet need for patients living with FL, particularly around access to newer, better-tolerated treatments, with the potential for longer remission and ultimately cure. Quality of life is a central priority for FL patients, alongside treatment effectiveness. Our patient insights show that treatment preferences are highly individual; shaped by the time of diagnosis, life stage, and personal experience. Many express a desire to avoid chemotherapy if possible, favouring immunotherapy or targeted treatments. However, a pragmatic approach is also important to them, prioritising efficacy and tolerability over treatment type alone. Information gaps remain a significant unmet need. In our Immunotherapy survey, patients rated their understanding of bispecific antibodies (and CAR-T) at just 2.16 out of 5. This knowledge gap was consistent across the top five countries of residence, including the UK. Patients told us the most valuable information relates to risks, side effects, effectiveness, and the treatment journey. Access is another major concern. In the UK, perceived barriers to bispecifics included limited availability, lack of approval, high costs, and questions around individual suitability. When considering treatment options, patients prioritised effectiveness while closely monitoring side effects, followed by effectiveness irrespective of side effects and their overall well-being—including financial impact and personal comfort. Together, these insights highlight the urgent need for more accessible, well-tolerated treatments, better patient education, and a more individualised, long-term approach to care.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	The biggest advantage is that it offers a new option for R/R FL patients. Whilst there are knowledge gaps in the patient community around bispecific antibodies, there is growing awareness and hope.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	Patients have expressed concerns around safety, especially in the longer term, and a recognised need for more clinical trial data to build confidence. The risk of side effects is a worry, and uncertainty remains high due to limited understanding within the patient community.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	This would be highly significant for those who have run out of treatment options and would be in line for systemic chemo or preparing to join a clinical trial.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	There is a concern that accessibility may be an issue – would this treatment potentially be only available in the larger hospital settings in a small number of locations across the country? How could all eligible patients access this treatment?

Other issues

13. Are there any other issues that you would like the committee to consider?	No

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• Patients with relapsed/refractory FL have limited treatment options, and patients are hopeful for a new option for R/R FL, in a space where there is very little available. • Epcoritamab activates the patient's own immune system to achieve high overall and complete response rates, along with manageable safety profile, making its potential approval a significant advancement in treatment. • Understanding of new treatments like bispecific antibodies is low; patients need clearer, more accessible information to make informed decisions. • While patients are hopeful about bispecific antibodies as a new option, concerns remain around safety, side effects, and the need for more clinical trial data and reassurance. • There is concern over accessibility, that no matter of location and background, eligible patients would be able to access this treatment.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

Patient organisation submission

Epcoritamab for treating relapsed or refractory follicular lymphoma after 2 or more systemic treatments [ID6338]

Please select YES if you would like to receive information about other NICE topics - **YES** or NO

For more information about how we process your personal data please see our [privacy notice](#).

Single Technology Appraisal
**Epcoritamab for treating relapsed or refractory follicular lymphoma after 2 or more
systemic treatments [ID6338]**

Patient Organisation Submission

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- Your response should not be longer than 10 pages.

About you

1. Your name	[REDACTED]
2. Name of organisation	Lymphoma Action
3. Job title or position	[REDACTED]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Lymphoma Action is a national charity, established in 1986, registered in England and Wales and in Scotland. We provide high quality information, advice and support to people affected by lymphoma – the 5th most common cancer in the UK. We also provide education, training and support to healthcare practitioners caring for lymphoma patients. In addition, we engage in policy and lobbying work at government level and within the National Health Service with the aim of improving the patient journey and experience of people affected by lymphoma. We are the only charity in the UK dedicated to lymphoma. Our mission is to make sure no one faces lymphoma alone. Lymphoma Action is not a membership organisation. We are funded from a variety of sources predominantly fundraising activity with some limited sponsorship and commercial activity. We have a policy for working with healthcare and pharmaceutical companies – those that provide products, drugs or services to patients on a commercial or profit-making basis. The total amount of financial support from healthcare companies will not exceed 20% of our total budgeted income for the financial year (this includes donations, gifts in kind, sponsorship etc) and a financial cap of £50,000 of support from individual healthcare companies per annum (excluding employee fundraising), unless approval to accept a higher amount is granted by the Board of Trustees.

	The policy and approach ensures that under no circumstances will these companies influence our strategic direction, activities or the content of the information we provide to people affected by lymphoma. https://lymphoma-action.org.uk/about-us-how-we-work-policies-and-terms-use/working-healthcare-and-pharmaceutical-companies
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] If so, please state the name of the company, amount, and purpose of funding.	• AbbVie £40,000 towards our information provision, helpline, workshops and preparing for treatment project • Bristol Myers Squibb £18,000 towards our support groups and our mission and objectives • Roche £40,000 towards our helpline, information provision, preparing for treatment project and peer support services
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	We spoke to members of our community to understand their experiences of living with follicular lymphoma. We combined the information gathered from this along with our experiences of working with these patients and their carers.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Lymphoma is a type of blood cancer where white blood cells known as lymphocytes grow out of control. It is the 5th most common type of cancer in the UK. There are two main types of lymphoma: non-Hodgkin lymphoma (NHL) and Hodgkin lymphoma (HL). NHL is the most prevalent, with around 14,200 people diagnosed each year in the UK. There are many different types of NHL which can be classified in two main ways. Firstly, they can be grouped into low-grade and high-grade based on how fast they grow. Secondly, they can be grouped depending on the type of lymphocyte they developed from: B cells or T cells. Follicular lymphoma (FL) is the most common type of NHL with 2,300 being diagnosed with it every year in the UK. It is a low-grade lymphoma developing from B cells. The B cells usually develop in clumps called follicles within the lymph nodes. FL can occur at any age but tends to be a lymphoma of older age with most cases occurring in people over the age of 60. These people are often thinking towards retirement and the diagnosis can be devastating as described here, <i>“Constant fear basically, it’s not the retirement we had planned and it’s devastating seeing the effect on my wife & family”</i>. In some people FL has no symptoms and the diagnosis is picked up incidentally when having investigations for something else. However, most people develop lumps, usually in their neck, armpits or groin. These are swollen lymph nodes. People can also experience weight loss, fevers, sweats, frequent infections and fatigue. As FL is a low-grade lymphoma these symptoms tend to develop gradually and it can often take a long time, and many appointments before a patient is diagnosed. Fatigue tends to be a particularly disabling symptom, and one which our patients find has a huge impact on their lives. <i>“Symptoms of fatigue, weight loss and loss of muscle mass with resulting physical weakness were severe enough to impact daily life...with consequent effects of day-to-day activities, hobbies and concentration, as well as impacting family finances and requiring increased support from family.”</i>

	<i>“My initial symptoms were severe fatigue, weight loss and night sweats.”</i> As well as the obvious physical impact, FL can have a profound impact on a patient’s emotional and mental wellbeing. It can be a very anxious time when adjusting to the new diagnosis, as well as waiting for the treatment and hoping that it will work. This psychological impact should not be underestimated. <i>“I ended up having anxiety/panic attacks due to trying to survive alone and with no income.”</i> <i>“It’s hard to plan anything or look ahead more than a couple of months and it has a big impact on finances just to add to the pressure... It’s a slow torture really, but you come to terms with it because you don’t have any choice.”</i> FL can be both staged, which indicates how advanced it is, and graded, which indicates how many large lymphocytes can be seen under a microscope. Grades 1,2 and 3A are all slow growing and are treated in a different way to grade 3B which is fast growing. Our patients reflected that low grade is often viewed as less serious because treatment may not be immediately required, and survival is better. However, by doing this people forget about the emotional burden that having an incurable cancer is. <i>“Because our illness is not curable we are left in active surveillance programmes. We know that the symptoms we deal with are not serious enough to justify toxic chemotherapy regimes and the chance of significant improvement is lower than the risk of side effects. Due to this we learn to minimise what we are dealing with and so it is often overlooked in our medical reviews as evidenced in the latest Lymphoma Coalition Survey.”</i> <i>“It’s hard to plan anything or look ahead more than a couple of months and it has a big impact on finances just to add to the pressure.”</i>

	When a person is diagnosed with FL this diagnosis does not just have an impact on them. They will have friends, spouses, children or grandchildren, and their lives can also be turned upside down. <i>“It’s absolutely awful for my wife. Her life has basically been ruined...she can no longer come with me to clinics or treatments, she did for the first few years but that has taken its toll and she now finds it too traumatic.”</i> <i>“My partner feels the same emotional impact of living with the uncertainty of an incurable cancer as I do. In addition, he has to deal with the financial and emotional impact of having to support me. His lifestyle, hobbies and activities are as altered as mine. I think the situation of a carer for someone with an incurable chronic cancer could be argued to be harder than that of the patient.”</i>

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	If a person is diagnosed with early-stage FL, which is about 1 in 5 people, they may not need to be started on treatment straightaway. People can go years like this in what is known as ‘active surveillance’, or ‘watch and wait’. Whilst people avoid the symptoms of active treatment it is still a very difficult time and can be referred to by patients as ‘worry and wait’. If treatment is required in early-stage disease this may be radiotherapy or rituximab antibody treatment. Most people at diagnosis have advanced stage disease. Despite this if they do not have troublesome symptoms, they may be treated the same as early-stage disease. If treatment is required, this is usually in the form of chemotherapy combined with antibody therapy. Chemoimmunotherapy, although often successful, can be very intense, requiring multiple visits to the hospital. It can also cause a number of short and long-term side effects such as fatigue, sickness, diarrhoea, hair loss and recurrent infections. <i>“Chemo caused many issues living alone. Feeling ill whilst alone is hard work (physically, emotionally and mentally). Still unable to work (self-employed) and unable to claim benefits added more stress.”</i> <i>“Chemo.....had the usual side effects of nausea, constipation, headaches, fatigue etc.”</i> If a patient responds well to chemoimmunotherapy they will usually be offered maintenance treatment. This involves having an injection of the antibody used in the chemoimmunotherapy every 2-3 months for up to 2 years. The aim of this is to keep the FL under control and make the remission period last as long as possible. This is because FL is unfortunately not curable, and almost everyone will relapse at some stage. Knowing that their disease is likely to come back whilst struggling with the side effects from treatment can be incredibly tough. <i>“There is an emotional impact both from dealing with these symptoms and their impact but also dealing with the knowledge that my type of lymphoma is currently incurable and carries a risk of transformation to a more aggressive form of lymphoma.”</i>

The treatment for relapsed disease depends on a number of things such as previous treatment used, the side-effects and impact of this treatment and how quickly the disease relapsed. Options for treatment are the same chemoimmunotherapy regimen, a different chemoimmunotherapy regimen, radiotherapy, obinutuzumab with bendamustine, or rituximab with the targeted treatment lenalidomide. If there is a good response to treatment, a course of higher dose chemotherapy with a stem cell transplant may be offered. One patient pointed out the effect repeated courses of chemotherapy can have, *“The need for repeated courses of chemotherapy can lead to cumulative toxicity which is particularly important as many patients can live for many years post treatment”*. Unfortunately, none of these treatments, even the most intense, will cure FL and relapse is likely to happen at some point. This knowledge can have a profound impact on the mental wellbeing of the patient and their loved ones.

“It’s also really terrifying to think I will probably run out of treatments one day, or a treatment available in the USA or EU might not be available to me, and the consultant will say no more can be done...It’s a slow torture really, but you come to terms with it because you don’t have any choice.”

“My quality of life has totally changed. I was a very fit self-employed person doing sprint triathlons, running, gym etc.”

“I know have to manage energy (as most of us do) I’m very weary of crowds, people with coughs etc Since I’ve relapsed for the 3rd time, I have no way of knowing if the treatments have been of any benefit.”

8. Is there an unmet need for patients with this condition?	Yes, patients strongly feel that there is an unmet need for a treatment which will cure the disease and remove the uncertainty that patients with FL have to live with. <i>“Follicular lymphoma patients have significant unmet needs as there are no available curative treatments.”</i> <i>“A perfect treatment would be a curative therapy with no long-term toxicity that would enable me to live a healthy future free of lymphoma and the worry of transformation.”</i> Patients also feel that there needs to be more options available to enable them to have choices available to them with as little long term side effects as possible. <i>“The most important thing of all for FL patients is that there are as many treatments as possible, because many of us are going to need them all.”</i> <i>“Much research data is understandably focused on overall survival but there is a significant unmet need for understanding of the symptom and psychological burden of a life with follicular lymphoma and the impact of post treatment effects of the currently offered regimens.”</i> <i>“I would welcome any opportunity to increase treatment options when I require treatment.”</i>

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	One clear advantage that our patients could identify is that epcoritamab is given subcutaneously. This is a much simpler method of administration than some of the current treatment options and would require fewer hospital appointments. <i>“The treatment regimen approved by the FDA would seem far less onerous for patients to endure and would consequently enable family and carers to also suffer less of a treatment burden.”</i> <i>“The fact that epcoritamab can be administered subcutaneously would also make it far more tolerable as a treatment.”</i> <i>“Delivery route of treatment becomes more critical with older age and the use of s/c administration could be a significant factor in tolerability of regimes in this group.”</i> <i>“As it’s a sub cut injection, this would be a simple fast treatment which could possibly be done at home, at a GP Surgery or as an outpatient.”</i> Patients also feel that epcoritamab can offer a treatment option with fewer side effects which is better tolerated. <i>“Reducing the risk of long-term chemotherapy toxicity by increasing regimen options with bispecifics would also be a considerable advantage for this group.”</i> This patient who received epcoritamab in a trial describes exactly what advantages he experienced: <i>“I’ve only been able to have Epcoritamab by being very lucky on a 50:50 randomised trial, we shouldn’t have to get lucky to receive a vital treatment when patients in the USA and EU can have them as standard. The treatment has been very straightforward for me, a bit like having a flu jab every week, not difficult at all and I’ve been able to work throughout. Much easier than chemo, and much, much easier</i>

	<i>than auto SCT. Only time will tell if it gives me longer before next relapse but at the very least it's another treatment with the chance of more time."</i>

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	Our patients could not think of any potential disadvantages of epcoritamab other than the side-effects but even these they felt were acceptable. <i>"I can't see any disadvantages to epcoritamab compared to being offered chemotherapy or CAR-T as the data on response rates and durability of treatment appear to be at very good levels and although there are risks of treatment with CRT being the main concern I would consider these acceptable particularly as treatments are available and the risk profile of CRT is increasingly understood."</i> <i>"Disadvantages could be some of the side effects, especially the ICANS. People living alone/elderly could find life difficult if they suffered with ICANS However..... having cancer can't be better than a few side effects."</i> Overall patients felt that any risks and disadvantages were outweighed by the advantages. <i>"I've driven 3,000 miles going to Manchester every week! - but I'd happily go every day if I had to."</i> <i>"There aren't really any disadvantages when you look at the incredible benefits."</i>

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	There was some disagreement amongst our patients as to who would benefit from this treatment most. One patient felt that older patients would benefit more: <i>“Delivery route of treatment becomes more critical with older age and the use of s/c administration could be a significant factor in tolerability of regimes in this group. Reducing the risk of long term chemotherapy toxicity by increasing regimen options with bispecifics would also be a considerable advantage for this group.”</i> However, this patient could see the benefits of the treatment in younger patients: <i>“Maybe younger patients would benefit due to the speed of treatments and general fitness levels.”</i> This demonstrates what an impact epcoritamab could have on a wide range of patients.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Our patients could not think of any potential equality issues.

Other issues

13. Are there any other issues that you would like the committee to consider?	All of our patients wanted the committee to consider the fact that there is an urgent need for further treatment options in the management of FL. One patient had this to say: <i>“I would like to see a more accurate cost analysis of epcoritamab that addresses the long-term costs of effects of other chemotherapy regimens and the psychosocial impact of complex prolonged cycles of treatment.”</i> It is also important to our patients that the committee understands the importance of having treatment options available which are well tolerated with few side effects. This was backed up by the recent Lymphoma Coalition survey. This survey on lymphomas was completed by 1204 UK respondents in 2024. Follicular lymphoma was the most common subtype reported (25%). The survey results reflected how important living as well as possible with lymphoma is to patients. Among the respondents, 93% selected 'improved quality of life' as one of the most important aspects of treatment, second only to 'improved / longer survival' and 'bring about a remission / response', both 96%. 'Fewer side effects / more tolerable side effects' during treatment was also a key consideration, selected by 72% of respondents.

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• Follicular lymphoma is the most common type of non-Hodgkin lymphoma • It is currently incurable, and all patients are likely to relapse after treatment • Current treatment options have a number of short- and long-term side effects • There is a need for further treatment options with less side effects and better responses • Epcoritamab is easy to administer and requires fewer hospital attendances.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

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Please select YES if you would like to receive information about other NICE topics - YES or NO

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Single Technology Appraisal

Epcoritamab for treating relapsed or refractory follicular lymphoma after 2 or more systemic treatments [ID6338]

Clinical expert statement

Information on completing this form

In [part 1](#) we are asking for your views on this technology. The text boxes will expand as you type.

In [part 2](#) we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

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Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Clinical expert statement

Epcoritamab for treating relapsed or refractory follicular lymphoma after 2 or more systemic treatments [ID6338]
of 12

Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See [Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals](#) (section 3.2) for more information.

The deadline for your response is **5pm on Friday 8 August 2025**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Part 1: Treating relapsed or refractory follicular lymphoma after 2 or more systemic treatments and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Kim Linton
2. Name of organisation	The University of Manchester and The Christie NHS Foundation Trust
3. Job title or position	Clinical Senior Lecturer
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with relapsed or refractory follicular lymphoma after 2 or more systemic treatments? ☐ A specialist in the clinical evidence base for relapsed or refractory follicular lymphoma after 2 or more systemic treatments or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	none

Clinical expert statement

8. What is the main aim of treatment for relapsed or refractory follicular lymphoma after 2 or more systemic treatments? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	To manage lymphoma symptoms and delay disease progression, whilst preserving or improving quality of life
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	High overall and complete response rates leading to prolonged progression free survival exceeding the median expected from standard therapy at later lines of therapy.
10. In your view, is there an unmet need for patients and healthcare professionals in relapsed or refractory follicular lymphoma after 2 or more systemic treatments?	Yes, many people have limited treatment options from 3L+ due to a) lack of available reimbursed options and b) refractoriness to standard therapies
11. How is relapsed or refractory follicular lymphoma after 2 or more systemic treatments currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	Most people need systemic therapy and receive either a) an approved therapy not previously received (if available and appropriate) such as immunochemotherapy or R2 or b) a clinical trial (if available and eligible). Some people have localised treatment e.g. palliative radiotherapy to symptomatic site(s). ESMO/EHA and BCSH guidelines are followed but the pathway is not well defined as there is no evidence to guide optimal choice or sequence of treatment. The technology offers a novel and additional line of therapy overcoming a) resistance to standard therapy b) exhaustion of standard therapy options
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	The technology is already used to treat relapsed/refractory DLBCL (NICE-approved indication). The technology will be used in the same way for relapsed/refractory follicular lymphoma.

Clinical expert statement

• How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	Healthcare resource differs from current care in the following ways a) treatment is delivered rapidly as a convenient subcutaneous injection, saving time on treatment days compared to standard iv chemo b) treatment is continuous until disease progression/toxicity unlike fixed duration chemo (however frequency is monthly after cycle 10), c) the toxicity profile is different to chemo with a need to monitor and manage CRS, however this is mostly low grade and staff are familiar with this from experience managing epcoritamab-treated DLBCL patients. The technology needs to be used in a specialist clinic however treatment is outpatient based and is moving towards a home care model Staff need to be trained on managing the side effects of T-cell engaging therapies. No specific equipment or facilities are needed apart from access to CCU for (rare) patients requiring support for high grade CRS or ICANs
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	Yes, indirect treatment comparisons between epcor and standard of care suggest significant, clinically meaningful benefits: 1) Sureda et al, Efficacy of Subcutaneous Epcoritamab vs Standard of Care (SCHOLAR-5) in Patients With Relapsed/Refractory Follicular Lymphoma After ≥2 Systemic Therapies: An Indirect Treatment Comparison, EHA 2025 (poster): - Epcor vs usual care: a. ORR 90.9% vs 56.8% b. CR 73.7% vs 32% c. PFS (adjusted hazard ratio [HR] 0.32 [95% CI: 0.186, 0.556]; $P<0.001$) – 68% reduction in risk of progression events or death d. OS (adjusted HR (95% CI) 0.31 (0.157, 0.627; $P=0.001$) – 68% reduction in risk of death

Clinical expert statement

	Patient reported outcomes and QoL are also favourable for epcoritamab: 1) Jurczak et al, Patient-Reported Outcomes in Patients With Relapsed or Refractory Follicular Lymphoma Treated With Epcoritamab, EHA 2025 (poster). This analysis evaluated patient-reported outcomes (PROs) related to symptoms of cancer and overall health-related quality of life (HRQoL) based on changes in the Functional Assessment of Cancer Therapy–Lymphoma (FACT-Lym) and the 3-level EQ-5D (EQ-5D-3L) among patients with FL receiving epcoritamab in the EPCORE NHL-1 study. Conclusions: a. Patients with R/R FL treated with Epcoritamab reported numerically increasing scores on multiple PRO assessments, suggesting maintenance of HRQoL while on treatment b. Among patients experiencing lymphoma symptoms at baseline, a substantial proportion reported symptom improvement while on treatment
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	This technology is expected to be effective for all patients with R/R FL including high risk FL (e.g. POD24, double refractory, last line refractory) and multiply relapsed (3/4L therapy) patients with historically dismal outcomes after standard treatment.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	Similar to use, especially for centres experienced with delivering bispecific antibodies, which is increasingly the case. Will need concomitant corticosteroids and adequate hydration to mitigate CRS for the first 4 doses of Epcoritamab (cycle 1), with additional monitoring for CRS in the first cycle of treatment. Will need infectious prophylaxis and monitoring of immunoglobulins during treatment with IVIG replacement therapy if IgG levels < 4 g/L at baseline or during treatment, or multiple infections.

Clinical expert statement

16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Therapy should be stopped early if patients experience unacceptable side effects such as recurrent infections on treatment despite antimicrobial prophylaxis +/- IVIG replacement therapy. Therapy will also be stopped if patients progress or in rare cases if they stop treatment to pursue allogeneic transplant.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	The treatment is very conveniently administered as a sc injection, offering advantages and improving the experience for patients and saving day unit time. The optimised dosing regimen allows for outpatient treatment without mandatory hospitalisation for CRS monitoring.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? - Is the technology a 'step-change' in the management of the condition? - Does the use of the technology address any particular unmet need of the patient population?	Yes, this is a step change medication offering a unique mode of action and treatment outcomes that are substantially better than expected from standard treatments from both anecdotal experience and indirect treatment comparisons. Epcoritamab address the clear unmet need to deliver more effective and well tolerated therapy at later lines of treatment to patients underserved with current treatments.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Most side effects are low grade and manageable. In the pivotal EPCORE NHL-1 trial, just 24 patients (19%) (of which 12 (9%) were due to covid-19) stopped treatment due to adverse events. Side effects did not adversely affect QoL in this study (see earlier QoL sub-analysis in Q13).
20. Do the clinical trials on the technology reflect current UK clinical practice?	Yes, the patient population is representative of UK patients. The most important outcomes are 1) high efficacy at all lines of therapy and in very high patients 2) an effective option for patients with poor performance

Clinical expert statement

• If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	status and/or organ impairment 3) manageable safety with further improvements using an optimised cycle 1 schedule. Complete metabolic response and duration of complete response are regarded as strong prognostic indicators for PFS and OS in R/R FL, although they are not perfectly reliable surrogates. No new adverse events have emerged since the pivotal trials.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	Yes, please see answers to Q13 for sub-analyses of the EPCORE NHL-1 published in abstract form
22. How do data on real-world experience compare with the trial data?	There are no published real-world studies or Epcoritamab in FL.
23. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could	No groups are disadvantaged or excluded.

Clinical expert statement

• exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	
24. The company's positioning for epcoritamab for patients in the fourth-line and beyond (4L+) setting. However, the EAG considers there is a strong rationale to include the broader population, as per the licence, of third-line and beyond (3L+). Would it be appropriate to accept the company's justification for positioning epcoritamab in the 4L+ setting, or is there also a strong unmet need in the 3L+ population that would support the EAG's broader positioning?	There is a strong unmet need at 3L as well as 4L+ and broader positioning is desirable, especially for patients with high-risk FL (POD24, double refractory, last line refractory) who will not do well with standard 3L treatment and for whom Epcoritamab has demonstrated effectiveness. Epcoritamab is also more effective in earlier lines (although still retains high CR rates ~50% in 5L+ therapy). The main challenge is demonstrating comparative effectiveness at 3L against available therapies, with comparisons against R2 being especially flawed due to the low-risk, mainly 2L population, enrolled in the AUGMENT trial and inability to adjust for lines of therapy in comparative analyses.
25. The company presented clinical evidence on the efficacy and safety of epcoritamab in the 4L+ setting from the EPCORE NHL-1 study and focused on adjusted analyses to account for COVID-19-related deaths. The EAG considers there are uncertainties with this adjustment. Is it appropriate to adjust for	It is absolutely appropriate to adjust for covid deaths in the analysis. This trial was conducted at the height of the pandemic and covid-19 represented the single biggest infectious mortality threat in living memory. An abstract submitted to the forthcoming SOHO 2025 conference compared outcomes for the pooled expansion cohort from the EPCORE NHL-1 FL and NHL-3 trials (EXP, n=149) for patients treated at the height of the pandemic (published in the EPCORE NHL-1 trial) and the optimisation cohort (OPT, n=86)

Clinical expert statement

COVID-19 deaths? Could this impact the reliability of the results?	for patients enrolled in the post-pandemic period. Results clearly illustrate the impact of covid-19 on trial outcomes in the pivotal NHL-1 trial, justifying the proposed adjustments. While response rates were similar (ORR/CR 84.6%/67.1% [EXP] vs 91.9%/73.3% [OPT]), safety was much improved, with significantly fewer high-grade infections and deaths post pandemic: OPT vs EXP: • G3-4 infections 34.9% (18.1% COVID-19) vs 20.9% (7% COVID-19) • G5 events 7.4% (5.4% COVID-19) vs 1.2% (0% COVID-19)
26. The company considered the most appropriate comparator was a basket of care in the 4L+ population. The company used the Haematological Malignancy Research Network (HMRN) dataset for use as a comparator in the matched adjusted indirect comparison (MAIC). Is the HMRN dataset an appropriate dataset for use as a comparator in the MAIC?	Yes, HMRN is an appropriate (albeit small) comparative dataset. There are currently no other published alternative control datasets. Foundation UK (Cl Linton) will report real world outcomes for 500 patients treated from 2L+ in relapsed and refractory FL in Q4 2025/Q1 2026.
27. The company assumed monthly haematologist consultant visits for the epcoritamab arm in the model. The EAG estimates that, in first month, haematologist consultant visits for the epcoritamab arm are weekly instead of monthly. What typically happens in clinical practice during that period?	Patients are reviewed weekly in the first 3 cycles, biweekly in cycles 4-9 and then monthly. Haematologist/oncologist review is required weekly in cycle 1, however can be stepped down to monthly from cycle 2 onwards with other visits can be done via protocol (nurse-led) clinics for (the majority of) patients who have not experienced significant toxicity.

Clinical expert statement

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

1. **Efficacy of Epcoritamab:** Epcoritamab offers clinically meaningful activity in patients with relapsed or refractory follicular lymphoma, achieving an overall response rate of 82% and a complete response rate of 62.5% in the pivotal cohort. Responses were observed across high-risk subgroups and heavily pretreated patients.
2. **Safety Profile:** Epcoritamab has a manageable safety profile, with most adverse events being low-grade. The cycle 1 optimisation cohort further reduces the incidence and severity of cytokine release syndrome, with no grade 3 or worse events reported in the trial, and eliminated mandatory hospitalisation for monitoring.
3. **MRD Negativity and Long-Term Outcomes:** High rates of measurable residual disease (MRD) negativity were observed in the trial, which were associated with improved progression-free survival, highlighting the potential for durable responses.
4. **Convenience of Subcutaneous Administration:** Epcoritamab's subcutaneous dosing offers practical advantages over intravenous therapies, improving patient experience and healthcare resource utilisation.
5. **Potential as a Novel Therapy:** Epcoritamab represents a promising alternative to current treatments for relapsed or refractory follicular lymphoma, with indirect treatment comparisons demonstrating clear benefits over standard treatments.

Clinical expert statement

Click or tap here to enter text.

Thank you for your time.

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Clinical expert statement

Epcoritamab for treating relapsed or refractory follicular lymphoma after 2 or more systemic treatments [ID6338]
of 12

Single Technology Appraisal

Epcoritamab for treating relapsed or refractory follicular lymphoma after 2 or more systemic treatments [ID6338]

Clinical expert statement

Information on completing this form

In [part 1](#) we are asking for your views on this technology. The text boxes will expand as you type.

In [part 2](#) we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Clinical expert statement

Epcoritamab for treating relapsed or refractory follicular lymphoma after 2 or more systemic treatments [ID6338]
of 10

Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See [Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals](#) (section 3.2) for more information.

The deadline for your response is **5pm on Friday 8 August 2025**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Part 1: Treating relapsed or refractory follicular lymphoma after 2 or more systemic treatments and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Mark Bishton
2. Name of organisation	University of Nottingham; Nottingham University Hospitals NHS Trust
3. Job title or position	Associate Professor and Honorary Consultant Haematologist
4. Are you (please tick all that apply)	☒ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with relapsed or refractory follicular lymphoma after 2 or more systemic treatments? ☒ A specialist in the clinical evidence base for relapsed or refractory follicular lymphoma after 2 or more systemic treatments or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A

Clinical expert statement

8. What is the main aim of treatment for relapsed or refractory follicular lymphoma after 2 or more systemic treatments? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	Most patients have incurable, advanced stage disease that follows a long relapsing/remitting course with progressively shorter remissions despite multiple lines of therapy. The primary treatment aim is to keep the disease at bay (progression free survival) whilst maintaining quality of life.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Complete metabolic response.
10. In your view, is there an unmet need for patients and healthcare professionals in relapsed or refractory follicular lymphoma after 2 or more systemic treatments?	Yes. Patients being treated third line or more have very limited options, are far more likely to fail to achieve remission, have short responses and experience cumulative complications.
11. How is relapsed or refractory follicular lymphoma after 2 or more systemic treatments currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	There are no standard treatment pathways, no randomised trials comparing experimental with current therapies, and limited outcome data from current therapy in rrFL. This has created immense difficulties around therapy choice and approval of novel agents. There are British Committee for standards in haematology (BCSH) guidelines although these are somewhat outdated and so not consider relapse to a great extent. There are two chemotherapy options CHOP/CVP and Bendamustine, and can be combined with either rituximab or Obinutuzumab monoclonal antibody for first line treatment. Antibody maintenance can be used. From second line onwards rituximab-lenalidomide is commissioned. These therapies are sequenced at the physicians discretion and so 2nd line+ therapies vary significantly. Dependant on the age and fitness of the patient, autologous stem cell transplantation, and those patients who did not receive maintenance antibody after first line immune-chemotherapy may receive following second (or third) line therapy. Epcoritamab would almost certainly be used preferentially to the above therapies for third line or greater treatment unless patients have already received bispecific antibodies as part of a clinical trial or compassionate access scheme.

Clinical expert statement

12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	Epcoritamab will be given in Daycase of level 2+ centres in secondary care. Smaller centres may have less experience with bispecific antibodies and refer to larger centres as seen with other, commissioned bispecific antibodies and given this pre-existing experience, no extra investment is required.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	Improvements in progression free survival will be seen and I believe there will be improvements in health-related quality of life more than current care. Improvements in overall survival are more difficult to predict given the long natural history of follicular lymphoma and current data, but I think likely.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient	High grade Cytokine release syndrome (CRS) is a rare but recognised specific complication, which clinicians need to be aware of. This is confined to cycles 1 and 2 in the vast majority of cases. Bispecific antibodies are already approved for other indications and its mitigation and management are well established.

Clinical expert statement

acceptability or ease of use or additional tests or monitoring needed)	Likewise late infections due to hypogammaglobulinaemia are established due to other treatment pathways, and its mitigation and management are well established.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Epcoritamab continues until disease progression or toxicity. It is likely that a significant number of patients may stop due to choice as well as recurrent infections but there are no formal rules.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	Epcoritamab is s/c and outreach programs may be set up, in contrast to normal therapies. The number of concomitant medications is less than with standard therapies.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? - Is the technology a 'step-change' in the management of the condition? - Does the use of the technology address any particular unmet need of the patient population?	Bispecific antibodies are considered 'game changing' for follicular lymphoma. There is no doubt that this new 'chemo free' class of drugs will progress to SoC for second line treatment globally when trial read out in the next 12-24 months, and ultimately first line for follicular lymphoma. The UK currently has no access to bispecific antibodies outside of clinical trials which only a tiny proportion of patients can access.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	High grade Cytokine release syndrome (CRS) is a rare (<5%) but recognised specific complication, which clinicians need to be aware of. This is confined to cycles 1 and 2 in the vast majority of cases and treatment algorithms are well established.

Clinical expert statement

	Otherwise, the treatment is extremely well tolerated. late infections due to hypogammaglobulinaemia are established due to other treatment pathways, and its mitigation and management are well established.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	To date, the only published data for Epcoritamab has been its evaluation in single arm studies. The primary endpoint for the pivotal cohort was overall response rate which for third line onwards treatment is acceptable. Progression free survival and adverse events which are the most relevant to the UK setting were key secondary endpoints, and showed excellent outcomes with low toxicity. The results can be extrapolated to the UK setting, especially as they were conducted and influenced by the covid 19 pandemic. No adverse effects that were not apparent in clinical trials have come to light.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No.
22. How do data on real-world experience compare with the trial data?	As a single arm study is being used for the appraisal this is difficult to answer. There is data for outcomes for third line or more follicular lymphoma – my biggest concern is that NICE will consider a single comparator eg R2 and do not consider that most patients will receive this second line and so all MAIC analyses are compromised.
23. NICE considers whether there are any equality issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.	There are no equality concerns.

Clinical expert statement

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	
24. The company's positioning for epcoritamab for patients in the fourth-line and beyond (4L+) setting. However, the EAG considers there is a strong rationale to include the broader population, as per the licence, of third-line and beyond (3L+). Would it be appropriate to accept the company's justification for positioning epcoritamab in the 4L+ setting, or is there also a strong unmet need in the 3L+ population that would support the EAG's broader positioning?	I believe the company have concerns based on the prior submission to NICE for mosunetuzumab, another bispecific antibody, in the same space. As mentioned above, the biggest concern is that NICE will consider a single comparator of the three main sequenced treatment options eg R2. R2 is off patent and cheap, however most patients currently receive it second line and so all MAIC analyses are inaccurate and the true cost effectiveness of epcoritamab hidden. By applying for fourth line the company wish to circumvent the problem which is very understandable.

Clinical expert statement

	I would be delighted to see epcoritamab commissioned third line or more and believe there is rationale based on the data but equally would rather commissioned fourth line than not at all.
25. The company presented clinical evidence on the efficacy and safety of epcoritamab in the 4L+ setting from the EPCORE NHL-1 study and focused on adjusted analyses to account for COVID-19-related deaths. The EAG considers there are uncertainties with this adjustment. Is it appropriate to adjust for COVID-19 deaths? Could this impact the reliability of the results?	The impact of covid has hugely reduced in the blood cancer population due to vaccination and natural immunity. There will always be uncertainties and this is best addressed by showing both adjusted and unadjusted analyses.
26. The company considered the most appropriate comparator was a basket of care in the 4L+ population. The company used the Haematological Malignancy Research Network (HMRN) dataset for use as a comparator in the matched adjusted indirect comparison (MAIC). Is the HMRN dataset an appropriate dataset for use as a comparator in the MAIC?	Yes - it is the largest dataset with granular data for this specific population. Numbers will be small but there are a limited number of patients nationally.
27. The company assumed monthly haematologist consultant visits for the epcoritamab arm in the model. The EAG estimates that, in first month, haematologist consultant visits for the epcoritamab arm are weekly instead of monthly. What typically happens in clinical practice during that period?	This will depend on individual clinicians. With CRS mitigation I personally see patients monthly as CRS will happen or not regardless of review.

Clinical expert statement

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Epcoritamab is a highly novel, game-changing therapy which provides a new treatment option for patients.

Epcoritamab is very well tolerated.

Comparator studies are very difficult to analyse credibly.

Many of the patients in the epcoritamab study will have received ALL or MOST of the regimens in the separate comparator studies already.

Thank you for your time.

Your privacy

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Clinical expert statement

Epcoritamab for treating relapsed or refractory follicular lymphoma after 2 or more systemic treatments [ID6338]
of 10

Single Technology Appraisal

Epcoritamab for treating relapsed or refractory follicular lymphoma after 2 or more systemic treatments [ID6338]

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

Information on completing this form

In [part 1](#) we are asking you about living with relapsed or refractory follicular lymphoma after 2 or more systemic treatments or caring for a patient with relapsed or refractory follicular lymphoma after 2 or more systemic treatments. The text boxes will expand as you type.

In [part 2](#) we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Patient expert statement

Epcoritamab for treating relapsed or refractory follicular lymphoma after 2 or more systemic treatments [ID6338]

Please use this questionnaire with our [hints and tips for patient experts](#). You can also refer to the [Patient Organisation submission guide](#). **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Your response should not be longer than 15 pages.

The deadline for your response is **5pm on Friday 8 August 2025**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Patient expert statement

Epcoritamab for treating relapsed or refractory follicular lymphoma after 2 or more systemic treatments [ID6338]

Part 1: Living with this condition or caring for a patient with relapsed or refractory follicular lymphoma after 2 or more systemic treatments

Table 1 About you, relapsed or refractory follicular lymphoma after 2 or more systemic treatments, current treatments and equality

1. Your name	Andy Brown
2. Are you (please tick all that apply)	☒ A patient with relapsed or refractory follicular lymphoma after 2 or more systemic treatments? ☒ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with relapsed or refractory follicular lymphoma after 2 or more systemic treatments? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Lymphoma Action
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and do not wish to complete a patient expert statement

Patient expert statement

Epcoritamab for treating relapsed or refractory follicular lymphoma after 2 or more systemic treatments [ID6338]

	☒ Yes, I was a contributor to my nominating organisations submission ☐ I agree with it and do not wish to complete this statement ☒ I agree with it and will be completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☒ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: I refer to one other patient I have contact with. ☐ I have completed part 2 of the statement after attending the expert engagement teleconference ☒ I have completed part 2 of the statement but was not able to attend the expert engagement teleconference (if that's the induction I'm having it soon) ☐ I have not completed part 2 of the statement
6. What is your experience of living with relapsed or refractory follicular lymphoma after 2 or more systemic treatments? If you are a carer (for someone with relapsed or refractory follicular lymphoma after 2 or more systemic treatments) please share your experience of caring for them	I've had follicular lymphoma since 2015. It is incurable. I've relapsed three times so far and I've had a lot of chemotherapy: RCVP plus maintenance, RCHOP, auto Stem Cell Transplant with BEAM, R2 (not chemo) and I'm now having immunotherapy with Epcoritamab plus Lenalidomide on the REFRACT trial at the Christie. I'm ten months into the trial. My scan at month three showed a complete metabolic response and that continued at month six. This is despite having extensive abdominal disease in numerous locations showing all the signs of transformation to high grade (though it hadn't) with the largest node 27cm. Epcoritamab is the easiest treatment I've had and I still can't quite believe my luck at randomising for it on the trial.

Patient expert statement

Epcoritamab for treating relapsed or refractory follicular lymphoma after 2 or more systemic treatments [ID6338]

	Follicular lymphoma is a living hell in many ways. Life is nothing like you planned and it's heartbreaking to see the impact on your wife and family. It's difficult to look more than three months ahead. Every scan is terrifying with the constant fear is of another relapse and then the sickening blow when it comes back. To add to the stress, it's very expensive being ill with months of no income. It's also tough to see others enjoying life, retirement, holidays and not living with endless worry. On the other hand, what's equally true, ten years on and I'm still here. This is much better than the alternative! You have to be strong for your family which is no bad thing. I refuse to let it spoil my day. I'm probably as optimistic now as I've ever been since diagnosis because the new immunotherapy treatments are coming through just in time. I've had most of the chemotherapies, now it's time for new and better drugs to increase the options available. Without new treatments I will run out of options. I'm lucky that I'm genetically optimistic. It would have been a real waste not to have made the best of those ten years, but it's a huge mental challenge. My wife can no longer come with me to clinics or treatments, she did for the first few years but that has taken its toll and she now finds it too traumatic. Her mental health is as badly affected as mine. I saw someone comment the other day "we watched our savings turn to dust". We sold our house after my first treatment and traded down so we had no mortgage. Only people who've been through all this will really understand how brutal it is.

Patient expert statement

Epcoritamab for treating relapsed or refractory follicular lymphoma after 2 or more systemic treatments [ID6338]

	Cumulative treatment time is significant. Even with the flexibility of self-employment, I estimate I've lost two years income so far at least. If I were an employee, it would have involved even more time off and you would need to have a very flexible employer. Physical work would be very difficult, as would something like teaching. I imagine many people would lose their job and find it very difficult to get another. Epcoritamab could significantly reduce time off work and enable patients to lead much more of a normal life.
7a. What do you think of the current treatments and care available for relapsed or refractory follicular lymphoma after 2 or more systemic treatments on the NHS? 7b. How do your views on these current treatments compare to those of other people that you may be aware of?	The chemo treatments have always worked well for me, but they've not kept it away for long. The big worry though is that treatments start to run out as they are not unlimited. Each relapse needs a new treatment, so the duration between is critical. This varies a lot. A patient diagnosed at 75 might only need one treatment and live a normal lifespan. A patient diagnosed at 55 and relapsing every two or three years will eventually run out of treatments and that assumes the chemo keeps working. After ten years I've had five treatments so far, one every two years on average, and now I only have two main chemo options left, B&R and RGDP. A donor stem cell transplant is also a possibility and there might come a point where that's worth a try as they are high risk. I will run out of options without immunotherapy. An additional worry is that I've had a lot of chemo which that must take its toll in some way but fortunately I've been ok so far, and obviously I wouldn't be here without it, but immunotherapy is going to be an incredibly important addition because of its effectiveness and lower toxicity.

Patient expert statement

Epcoritamab for treating relapsed or refractory follicular lymphoma after 2 or more systemic treatments [ID6338]

8. If there are disadvantages for patients of current NHS treatments for relapsed or refractory follicular lymphoma after 2 or more systemic treatments (for example, how they are given or taken, side effects of treatment, and any others) please describe these	The main disadvantages of the current treatments are how physically demanding they can be, plus the collateral damage from chemo and the length of time the treatments take in terms of disrupted life and lost income. Also, each chemo can normally only be used once. As I've had the five treatments so far, without the new immunotherapies I'd be lucky to get another five years with the current regimens because I would have had all the chemotherapy available. And that's assuming they keep working. Epcoritamab would extend my life with no detriment to quality. I've been ok with side effects and avoided any emergency hospital admissions, but I've spent many, many hours connected to IV drips and in treatment rooms. Treatments are lengthy. RCVP was six cycles every three weeks, a full day for each and a few days to recover. I imagine many people would take the 18 weeks off completely, but we are self-employed so you have to do as much work as you can. I probably had three or four days off per cycle, though more at the start because I had a chest drain in place for six weeks. RCHOP is another six cycles but it's more demanding, I managed to work quite a bit but for an employee it would be difficult. A physical job wouldn't really be possible. The infection risk means you wouldn't want to be teaching say or working in a busy office, or even commuting on public transport. So that's five months off work for most people I imagine, certainly so for most sorts of work.

Patient expert statement

Epcoritamab for treating relapsed or refractory follicular lymphoma after 2 or more systemic treatments [ID6338]

	Stem cell transplants are very tough, that was my third treatment. I was in hospital for 28 days and it took more than two months to get my strength back afterwards. I had to rest half-way up the stairs when I first came home. I reckon a minimum of three months off work in total even for the self-employed. It's also mentally challenging to say the least, 21 days in an isolation room for your immune system to rebuild is really hard mentally.
9a. If there are advantages of epcoritamab over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? 9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why? 9c. Does epcoritamab help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these	Epcoritamab is absolutely incredible. The ease of treatment is a big advantage but of course the effectiveness is what really counts. The subcutaneous injections literally take minutes. Each treatment just takes a morning on the trial, first a blood test, then see the Dr in clinic, wait a little while for the injection to be prepared, then five minutes in the treatment chair and heading home. There are 21 injections in total, I've had 19 so far, the first 12 are weekly followed by a further 9 every four weeks. The complete treatment is 48 weeks. Ease of treatment must be a big saving for the NHS, the injections could be given at your local GP surgery one day. The ultimate aim should surely be to use Epcoritamab as a first line treatment. That means I've needed just 21 days off work over the 48 weeks. The Christie is a two hour drive for me, but if the treatment was local it would be just half a day off and I could do desk work in the afternoon. I can easily drive myself and because it's so straightforward it's much less stressful for my wife to live through it. Our work is less interrupted than previously and life is much closer to being normal than with chemo. I've had no side effects with Epcoritamab and I understand they are rare anyway. Being able to work throughout the treatment is a huge advantage

Patient expert statement

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	financially and for mental wellbeing. I'm semi-retired and I help my wife with her curtains and blinds business which is partly admin and partly physical, fitting poles and hanging curtains etc. It's good to keep active and busy, distraction therapy works well. I also understand Bispecifics such as Epcoritamab can be used more than once. This is potentially a huge advantage. They are also less toxic, meaning less collateral damage. Many patients have other health issues, immunotherapy must surely help make treatment easier for them. I imagine that using Epcoritamab instead of chemotherapy could push back the need for the more lengthy and costly treatments such as stem cell transplants and CAR-T. I could see that being a big cost saving. I guess CAR-T will eventually replace most stem cell transplants. It's hard to say which is the most important advantage. It must still be early days for long term effectiveness to mature. But adding them all together means Epcoritamab is definitely the game-changer people say.
10. If there are disadvantages of epcoritamab over current treatments on the NHS please describe these. For example, are there any risks with epcoritamab? If you are concerned about any potential side effects you have heard about, please describe them and explain why	None really. Maybe it's a possibility that a patient might have difficulty with CRS or ICANS (neurological side effects) but that seems unlikely from what I hear. It's also possible that Epcoritamab might not work, but then there's still chemo, so I don't see any disadvantages to someone trying it, there's only upside.

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11. Are there any groups of patients who might benefit more from epcoritamab or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	All patients will benefit. Patients with comorbidities will benefit, as will older patients who just find treatment more difficult, but so will younger patients with no other health issues because treatment will be quicker and easier, meaning less time in the hospital and the treatment room, and less time off work.
12. Are there any potential equality issues that should be taken into account when considering relapsed or refractory follicular lymphoma after 2 or more systemic treatments and epcoritamab? Please explain if you think any groups of people with this condition are particularly disadvantage Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	I don't think so.
13. Are there any other issues that you would like the committee to consider?	1) Around 20% of follicular lymphoma patients have difficult to treat disease which relapses more frequently and grows more aggressively, mine included. All FL patients should have the benefit of Epcoritamab when treatment is needed, but the 20% currently have a really urgent need.

Patient expert statement

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	For example, I am in contact with an early forties FL patient with difficult disease. After treatment with RCHOP their disease relapsed within 24 months. A trial randomised to R2 instead of the bispecific. That failed and treatment is now RGDP, mostly as an inpatient at the moment. Disease has reduced but not by much and an allogenic transplant or trial is being discussed. Options are running out and the chance of trying Epcoritamab or CAR-T is desperately needed. Apart from the obvious justification on compassionate grounds, surely there's a potential cost saving here as well by trying Epcoritamab early on in such situations? Weeks in hospital potentially saved, particularly if a transplant is avoided. Surely Epcoritamab becomes possibly the lowest cost option to try for many patients like this? 2) Could just two Epcoritamab treatments give me ten more years compared to having existing regimens only? If I hadn't randomised for Epcoritamab this time I would have had Bendamustine chemo, with the most likely outcome being a further five years survival at the most. The five years being based on having RGDP after that, and maybe RCVP again as well, or the chance of a donor stem cell transplant, but with no Bispecifics. However, if including Bispecifics, future treatment could be: Complete the current Epcoritamab trial. Bendamustine chemo at next relapse. Epcoritamab at the following relapse. RGDP chemo at the relapse after that.

Patient expert statement

Epcoritamab for treating relapsed or refractory follicular lymphoma after 2 or more systemic treatments [ID6338]

	CAR-T after that? Or donor stem cells, or RCVP again. With my optimistic patient logic, two Epcoritamab treatments could add ten years to my potential lifespan, ie fifteen years from now with Epcoritamab versus five without. The new treatment versus old treatment calculation looks at it differently, my point is that I'm likely to need both. The appraisal process looks at Epcoritamab versus existing chemo treatment. But what if the chemo works well too? Is there a chance Epcoritamab might be ruled out because the chemo works well anyway? Whereas adding just two Epcoritamab treatments could potentially give me ten more years compared to existing treatments only.

Patient expert statement

Epcoritamab for treating relapsed or refractory follicular lymphoma after 2 or more systemic treatments [ID6338]

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- **Epcoritamab is the easiest and quickest treatment I've had, meaning savings for the NHS and patients.**
- **There are two types of FL patient; those who have some treatment and live a normal lifespan and those who will need every treatment available, Epcoritamab is urgently needed to add life-saving options for those needing them.**
- **Epcoritamab is 21 injections which could be given at your GP, versus six or eight days chemo, or versus a 28 day inpatient stem cell transplant, meaning lower treatment costs with much improved quality of life.**
- **Epcoritamab should be used for all FL patients, but the 20% with difficult disease need it very urgently, I had a complete metabolic response after three months despite extensive and aggressive disease.**
- **The ultimate aim must be use Epcoritamab as a first line treatment, immunotherapy is the future.**

Thank you for your time.

Patient expert statement

Epcoritamab for treating relapsed or refractory follicular lymphoma after 2 or more systemic treatments [ID6338]

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Patient expert statement

Epcoritamab for treating relapsed or refractory follicular lymphoma after 2 or more systemic treatments [ID6338]

Epcoritamab for treating relapsed or refractory follicular lymphoma after 2 or more systemic treatments [ID6338]

External Assessment Group (EAG) report

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Rider on responsibility for report

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Contributions of authors

Christiana Anyebe reviewed the cost-effectiveness evidence and undertook EAG's economic modelling. Mubarak Patel and Daniel Gallacher critiqued the company survival analysis and conducted EAG additional analysis. Emma Loveman and Angela Mwape reviewed the clinical evidence. Jill Colquitt supported the reviewed of the clinical evidence. Anna Brown reviewed the company's literature searches and conducted additional searches. Mandy Maredza coordinated the project and supported the critique of the cost-effectiveness evidence. All authors read and accepted the final report.

Please note that: Sections highlighted in aqua and underlined are 'commercial in confidence' (CIC). Figures that are CIC have been bordered with blue. Depersonalised Data (DPD) is highlighted in pink.

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Executive Summary

1 Executive summary

This summary provides a brief overview of the key issues identified by the External Assessment Group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.6 explain the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main EAG report.

All issues identified represent the EAG's view, not the opinion of NICE.

1.1 Overview of the EAG's key issues

Table 1: Summary of key issues

ID6338	Summary of issue	Report sections
1	Restriction to fourth line or more (4L+). The population in the company's decision problem is narrower than the NICE scoped population and UK marketing authorisation.	2.3. 2.2.2, Table 3
2	Evidence uncertainty from the included epcoritamab study. There are limitations with the epcoritamab study in terms of data-cuts, analyses, and generalisability.	3.2.2, 3.2.3, Table 8, 3.2.5, 3.2.6,3.2.7
3	Appropriateness of the comparator data set. There are differences between the sources of evidence for epcoritamab and the chosen comparator	3.4
4	Use of covid-adjusted data to model PFS and OS for epcoritamab Company uses data from the EPCORE NHL-1 study, censored for Covid deaths, to estimate PFS and OS resulting in extrapolations that appear overly optimistic.	4.2.6.1
5	Source of evidence and modelling of efficacy in comparator arm	3.4, 4.2.6

ID6338	Summary of issue	Report sections
	Modelling of efficacy for the comparator (current 4L+ care) in the economic model based on application of hazard ratios (to OS and PFS) derived from the company's preferred matched adjusted indirect comparison (MAIC). The EAG has concerns over the suitability of the MAIC performed.	
6	Suitability of approach to estimating health state utilities in PFS state of comparator arm PFS utilities applied in economic model differ between epcoritamab and comparator arm. The EAG has concerns over the suitability of the company's approach to weight PFS utilities from EPCORE NHL-1 by complete response status only, without accounting for any other variables and, potentially, the time patients spend in CR status.	4.2.7.3
7	Approach to costing adverse events in economic model may overestimate adverse events costs in comparator arm The company uses incidence data for R-CHOP from RELEVANCE trial, which reports high incidence of neutropenia to represent adverse events for the basket of care included in current 4L+ care.	4.2.7.4
Other Issues		
Issue 8	Resource use may be slightly underestimated in Epcoritamab arm Haematologist consultant visits may be slightly underestimated for Epcoritamab in the economic model	4.2.8.4
Issue 9	Costs of subsequent CAR-T therapy in Epcoritamab arm not captured in the economic model potentially underestimating the total costs of Epcoritamab The company did not censor [REDACTED] patients who received CAR-T as subsequent therapy in the economic model (potential benefits potentially captured in Epcoritamab arm), but the costs of subsequent CAR-T therapy not explored	4.2.8.3
Issue10	Severity weighting It is uncertain whether a severity modifier should apply for this appraisal based on differences in EAG's and company's QALY shortfall results.	4.2.9

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are as follows:

- The EAG prefers to use a naïve comparison to inform relative efficacy of epcoritamab. In this approach, the PFS and OS outcomes for current 4L+

care are directly extrapolated from HMRN data, without the use of a MAIC. For epcoritamab, data that are not adjusted for Covid deaths are used in the naïve comparison, to maintain consistency with the unadjusted HMRN data. Other differences include:

- Application of same utility weights for PFS, in both treatment arms, without adjusting for complete response status
- Incidence of AEs in current 4L+ care estimated based on weighted AE incidence for O-Benda, R-CHOP and R² instead of R-CHOP only.
- Increased haematologist's consultant visits in first month for Epcoritamab arm.
- No severity weighting

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Utility values assigned to the different health states
- Source of data and method of informing relative efficacy
 - Relative efficacy is informed using a naïve comparison between epcoritamab and the HMRN 4L+ FL data. Epcoritamab outcomes are based on EPCORE NHL-1 study data, unadjusted for COVID-19 deaths, while comparator outcomes are directly extrapolated from observational HRMN data without adjustment or indirect treatment comparison.

Overall, the technology is modelled to affect costs by:

- Source of data and method of informing relative efficacy
 - Costs are influenced by treatment duration and health state occupancy, which are informed by progression-free survival, overall survival, and time to

treatment discontinuation from the EPCORE NHL-1 study for epcoritamab and the HRMN observational real-world data for the comparator arm.

- Frequency of adverse events

The modelling assumptions that have the greatest effect on the ICER are:

- Estimating PFS and OS outcomes for comparator (current 4L+ care) directly from HMRN data and informing relative efficacy via a naïve comparison

1.3 *The decision problem: summary of the EAG's key issues*

Issue 1: Restriction to 4L+ population

Report section	2.3
Description of issue and why the EAG has identified it as important	The company's positioning for epcoritamab for patients in the fourth-line and beyond (4L+) setting. However, based on the clinical evidence and clinical expert advice of the unmet need the EAG considers there is a strong rationale to include the broader population, as per the anticipated licence ₁ of third-line and beyond (3L+). The EAG also considers that best supportive care (BSC) is an appropriate comparator but no evidence was identified.
What alternative approach has the EAG suggested?	The EAG has reported the available evidence of epcoritamab in the 3L+ setting.
What is the expected effect on the cost-effectiveness estimates?	Unknown
What additional evidence or analyses might help to resolve this key issue?	To consider potential sources of evidence for the comparator at 3L+.

1.4 *The clinical effectiveness evidence: summary of the EAG's key issues*

Issue 2: Evidence uncertainty from the included epcoritamab study

Report section	3.2
Description of issue and why the EAG has identified it as important	There are limitations with the epcoritamab study. EPCORE NHL-1 is an ongoing, single-arm, open-label trial. The data are from subgroups relating to number of prior lines of treatment and some data from the latest data cuts could not be validated. It has not been possible to fully validate all data in the CS. The company focus on adjusted analyses to account for COVID-19 deaths, but also presented un-adjusted analyses. The EAG consider there are uncertainties with the COVID-19 adjustment (discussed in issue 4). These limitations combined with heterogeneity in the patient population raise questions about the generalisability of the findings to the broader population of patients with relapsed/refractory FL in routine clinical practice.
What alternative approach has the EAG suggested?	The EAG has explored the issues relating to number of prior lines of treatment and the COVID-19 adjustment by presenting both sets of data but is unable to meaningfully explore the impact of the other concerns (uncertain generalisability).
What is the expected effect on the cost-effectiveness estimates?	██████ in ICER for the Covid adjustment. Impact on other issues unknown
What additional evidence or analyses might help to resolve this key issue?	With the current evidence base the EAG is unable to offer any further insight into how to reduce the uncertainty in the data. A UK based study would help reduce the uncertainty around generalisability.

Issue 3: Appropriateness of HMRN dataset as comparator

Report section	3.4.1, 3.4.2
Description of issue and why the EAG has identified it as important	There are several important differences between EPCORE-1 and the HMRN dataset, including study design, years of conduct and length of follow-up, and participant characteristics, including treatment effect modifiers such as prior treatments. These raise concerns regarding the validity of the company's MAIC.
What alternative approach has the EAG suggested?	The EAG has conducted additional searches but no alternative comparator has been identified.
What is the expected effect on the cost-effectiveness estimates?	Unknown
What additional evidence or analyses might help to resolve this key issue?	Further evidence from a more similar data set would reduce uncertainty.

Issue 4: Use of covid-adjusted data to model PFS and OS for epcoritamab

Report section	4.2.6.1
Description of issue and why the EAG has identified it as important	Company uses data from the EPCORE NHL-1 study, censored for Covid deaths, to estimate PFS and OS resulting in extrapolations that appear overly optimistic according to EAG's clinical experts' opinions.
What alternative approach has the EAG suggested?	The EAG prefers to use the COVID-unmodified data from EPCORE NHL-1 for PFS and OS whilst maintaining the company's choice of extrapolations (log-normal) for both PFS and OS, to ensure consistency with the HMRN data, which has not been adjusted for COVID-19 deaths.
What is the expected effect on the cost-effectiveness estimates?	██████ in ICER
What additional evidence or analyses might help to resolve this key issue?	Additional information on Covid or Covid deaths in HMRN dataset could provide evidence to justify use of Covid-modified or unmodified data in the current appraisal

Issue 5: Source of evidence and modelling of efficacy in comparator arm

Report section	4.2.6.1
Description of issue and why the EAG has identified it as important	Modelling of efficacy for the comparator (current 4L+ care) in the economic model based on application of hazard ratios (to OS and PFS) derived from the company's preferred MAIC. The EAG has concerns over the suitability of the MAIC performed due to: (i) potential for relative efficacy estimates being biased by outcomes of a small number of individuals due to small sample sizes of the MAIC weighted population (██████) and HMRN cohort (██████); (ii) stricter inclusion/exclusion criteria of the EPCORE NHL-1 trial means methodology of MAIC is unlikely to account for the differences between a trial and real-world population. It is notable that, the MAIC adjustment resulted in hazard ratios that favoured ██████████ than in the unadjusted analysis. While the direction of change following adjustment is not always predictable, this result was not expected. This further calls into question the face validity of the MAIC results.
What alternative approach has the EAG suggested?	The EAG prefers to use a naïve comparison to inform relative efficacy. The PFS and OS outcomes of current 4L+ care are directly extrapolated from HMRN data rather than using HR derived via a MAIC.
What is the expected effect on the cost-effectiveness estimates?	██████ in ICER
What additional evidence or analyses might help to resolve this key issue?	A larger real-world comparator cohort with more complete data on key prognostic variables could improve the validity of an adjusted comparison. Furthermore, better transparency around missing data and COVID-19 impact

	in both arms would strengthen the case for an indirect treatment comparison.

1.5 *The cost-effectiveness evidence: summary of the EAG's key issues*

- The company's review of cost-effectiveness evidence was reasonable, but contained some limitations detailed in Section 4.2
- The company submitted a simple *de novo* cost-utility model using partitioned survival with a weekly cycle length and a 35.2-year time horizon. See Section 4.2.2 for our critique.

The EAG's concerns regarding the MAIC analysis used to estimate relative efficacy generate uncertainty in the results of cost-effectiveness analysis (see Sections 4.2.6 and 6.3).

Issue 6: Suitability of approach to estimating health state utilities in PFS state of comparator arm

Report section	4.2.7.3
Description of issue and why the EAG has identified it as important	PFS utilities applied in economic model differ between epcoritamab and comparator arm. The EAG has concerns over the suitability of the company's approach to weight PFS utilities from EPCORE NHL-1 by complete response status only, without accounting for any other variables and, potentially, the time patients spend in CR status
What alternative approach has the EAG suggested?	The EAG prefers to apply the same utility weights for PFS for both treatment arms, i.e., utilities derived via EQ-5D in EPCORE NHL-1 trial but not adjusted for complete response status
What is the expected effect on the cost-effectiveness estimates?	██████ in ICER
What additional evidence or analyses might help to resolve this key issue?	Additional mixed regression analyses that explore inclusion of other variables e.g., adverse events and/or time spent in CR in PFS state might provide additional layer of evidence to justify choice of approach

Issue 7: Approach to costing adverse events in economic model may overestimate adverse events costs in comparator arm

Report section	3.2.7.4
Description of issue and why the EAG has identified it as important	The company uses incidence data for R-CHOP from RELEVANCE trial, which reports high incidence of neutropenia to represent adverse events for the basket of care included in current 4L+ care arm and this overestimates AE costs in the comparator arm.
What alternative approach has the EAG suggested?	The EAG prefers to use weighted incidence based on data for O-Benda, R-CHOP and R ² instead of data for R-CHOP only.
What is the expected effect on the cost-effectiveness estimates?	██████ in ICER
What additional evidence or analyses might help to resolve this key issue?	Future real world-evidence on incidence of AEs in this patient population might provide useful additional data that reflects AE rates observed in clinical practice

1.6 Other key issues: summary of the EAG's view

In addition to the key issues outlined in Section 1.1, the EAG note the following two 'other issues'.

Issue 8: Resource use may be slightly underestimated in Epcoritamab arm

Report section	4.2.8.4
Description of issue and why the EAG has identified it as important	Haematologist consultant visits may be slightly underestimated for Epcoritamab arm in the economic model according to EAG's clinical experts' opinions.
What alternative approach has the EAG suggested?	The EAG estimates that, in first month, haematologist consultant visits for Epcoritamab arm are weekly instead of company's assumption of monthly visit in first month. The same assumptions as the company's are maintained from month 2 onwards.
What is the expected effect on the cost-effectiveness estimates?	██████ in ICER
What additional evidence or analyses might help to resolve this key issue?	None

Issue 9: Costs of subsequent CAR-T therapy in Epcoritamab arm not captured in the economic model potentially underestimating the total costs of Epcoritamab

Report section	4.2.8.3
Description of issue and why the EAG has identified it as important	The company did not censor [REDACTED] patients who received CAR-T as subsequent therapy in the economic model (potential benefits potentially captured in Epcoritamab arm), but the costs of subsequent CAR-T therapy not explored
What alternative approach has the EAG suggested?	The EAG did not propose an alternative approach
What is the expected effect on the cost-effectiveness estimates?	Potentially, [REDACTED] in ICER
What additional evidence or analyses might help to resolve this key issue?	Additional scenario analyses censoring patients who received CAR-T as subsequent therapy OR scenario analysis including CAR-T costs when offered as subsequent therapy could better reflect experiences from the EPCORE NHL-1 study.

Issue 10: Severity weighting

Report section	
Description of issue and why the EAG has identified it as important	The EAG's base case analysis estimates higher QALY gains in current 4L+ care compared to company's analysis. The proportional and QALY shortfall calculations therefore indicate that a severity weight should not be applied for this appraisal.
What alternative approach has the EAG suggested?	None
What is the expected effect on the cost-effectiveness estimates?	██████ in ICER
What additional evidence or analyses might help to resolve this key issue?	Resolving the uncertainty in estimating efficacy of current 4L+ care (discussed in key issue 5). QALYs generated by patients on current treatment are needed to accurately determine the severity of disease, or QALY shortfalls (when QALYs are compared against general population)

1.7 Summary of EAG's preferred assumptions and resulting ICER

Table 2 outlines the EAG's preferred assumptions with changes to each assumption from the company's base case presented individually. We present numerical estimates of the resulting ICERs in an incremental analysis and indicate the change from the company's base case ICERs.

Table 2: Summary of EAG's preferred assumptions and ICER

Preferred assumption	Section in EAG report	Incremental Costs	Incremental QALYs	ICER £/QALY	Change in ICER n (%)
Company's base case		██████	3.994	██████	
*Correction for LDH cost application for PFS state ^a	4.2.8.4	██████	3.994	██████	
<i>Survival modelling approach for epcoritamab and current 4L+ care</i>					
Epcoritamab:					

Preferred assumption	Section in EAG report	Incremental Costs	Incremental QALYs	ICER £/QALY	Change in ICER n (%)
EAG 01: Log-normal extrapolations for PFS and OS for epcoritamab based on <i>Covid unadjusted data</i> from EPCORE NHL - 1 ^b	4.2.6.1	██████	2.862	██████████	██████████
Current 4L+ Care:					
EAG 02: Log-normal extrapolations for both PFS and OS for current 4L+ care using HMRN data directly ^c	4.2.6.1	██████████	3.286	██████████	██████████
Cumulative impact of EAG 01 – EAG 02 (naïve analysis)	4.2.6.1.1 6.1	██████	1.709	██████	██████████
<i>Alternative resource usage</i>					
EAG 03: Higher frequency of haematologist consultant visits in the first month in epcoritamab arm	4.2.8.4	██████	3.994	██████	██████████
<i>Utilities for PFS and PD</i>					
EAG 04: Utilities for PFS from EPCORE NHL-1 trial, adjusted for PD using wild et al		██████	4.127	██████	██████████
<i>Adverse events</i>					
EAG 05: Adverse events incidence in comparator arm based on reweighted data for R-CHOP (RELEVANCE), O-Benda (GADOLIN) and R ² (MAGNIFY) as reported in TA894 ^d	4.2.7.4	██████	3.994	██████	██████████

Preferred assumption	Section in EAG report	Incremental Costs	Incremental QALYs	ICER £/QALY	Change in ICER n (%)
EAG 06: Inclusion of grade 2 CRS events requiring treatment with tocilizumab	4.2.7.4 4.2.8.5	██████	3.994	██████	██████████
Cumulative impact of all changes (EAG01 – EAG06)^e		██████████	1.427	██████████	██████████
Sensitivity Analysis: Cumulative impact of all changes (EAG01 – EAG06)^f		██████████	1.71	██████████	██████████
^a Change in ICER calculated based on corrected company's base case ICER of ██████ ^b Company's base case analysis uses covid-modified data but choice of extrapolations (log-normal) is the same as in EAG's base case ^c Company applies HRs obtained from their preferred MAIC to the PFS and OS extrapolations of epcoritamab ^d Company uses data for R-CHOP only ^e EAG base case does not apply severity modifier ^f Sensitivity analysis: x1.2 severity modifier applied to incremental QALYs. This is similar to comparing the EAG's base ICER with company's severity unadjusted (corrected) ICER of ██████					

The EAG corrected an error in the company's economic model related to costs of lactate dehydrogenase (LDH) test and the EAG's preferred base case incorporates this change (see section 4.2.8.4).

Acronyms Table

3L+	Third line plus
4L+	Fourth line plus
allo-SCT	Allogeneic stem cell transplant
B2M	beta-2 microglobulin
BSC	Best supportive care
BSH	British Society of Haematology
CAR-T	chimeric antigen receptor T-cell therapy
CEM	Cost-effectiveness Model
CIT	chemotherapy induced therapy
CR	Complete response
CRS	Cytokine release syndrome
CS	Company Submission
CSR	Clinical Study Report
DLBCL	diffuse large b-cell lymphoma
DOCR	Duration of complete response
DOR	Duration of Response
EAG	Evidence Assessment Group
ESS	Effective Sample Size
FACT-G	general quality of life instrument
FACT-LymS	Functional Assessment of Cancer Therapy-Lymphoma subscale
FIH	first-in-human
FL	Follicular lymphoma
FL grade 3B	follicular lymphoma, grade 3b
FLIPI	Follicular Lymphoma International Prognostic Index
HGBCL	high-grade b-cell lymphoma
HMRN	Haematological Malignancy Research Network
HRQoL	Health-related quality of life
ICERs	incremental cost-effectiveness ratios
IRC	independent review committee
KM	Kaplan Meir
LDH	lactate dehydrogenase
LMM	Linear mixed model
LYRIC	Lymphoma Response to Immunomodulatory Therapy Criteria
MA	Marketing authorisation
MCL	mantle cell lymphoma
MHRA	Medicines and Healthcare Products Regulatory Agency
MID	Minimum Important Difference
MZL	marginal zone lymphoma
NHL	non-Hodgkin lymphoma
NICE	National Institute for Health and Care Excellence
ORR	overall response rate
OS	Overall survival

PD	Progressed disease
PFS	Progression-free survival
PMBCL	primary mediastinal b-cell lymphoma
POD24	progression of disease within 24 months
PSM	partitioned survival model
R/R	Relapsed/Refractory
R2	lenalidomide with rituximab
RCTs	randomised controlled trials
RWE	Real World Evidence
sc	Subcutaneously
SCT	simulated treatment comparison
SLL	small lymphocytic lymphoma
SLRs	systematic literature reviews
TA	Techology Appraisal
TEAE	Treatment Emergent Adverse Events
TOI	Trial Outcome Index
TTD	Time to discontinuation
TTNT	Time to Next Lymphoma Therapy
TTR	Time to Response
WTP	Willingness to Pay

External Assessment Group Report

2 INTRODUCTION AND BACKGROUND

2.1 *Introduction*

The EAG has reviewed and critiqued the company submission (CS) submitted to NICE by AbbVie Ltd. This report evaluates the clinical and cost-effectiveness evidence for epcoritamab (Tepkinly) in treating adult patients with relapsed or refractory (R/R) follicular lymphoma (FL) grade 1 – 3A, after three or more prior lines (4L+) of systemic treatments.

2.2 *Background*

2.2.1 **Background to the condition**

The company provides a description of epcoritamab and of the relevant health condition (B.1.2 – 1.3), however, some citations were either inaccurately represented or lacked sufficient context as discussed below. This section provides a critique of the company overview of the disease, the technology, and the positioning of epcoritamab within the treatment pathway.

Follicular lymphoma

The CS cites relevant references in their description of the health condition (B.1.3.1). FL is a type of non-Hodgkin lymphoma (NHL) that is a mature B-cell-derived, indolent disease (with the exception of grade 3B, which is more aggressive) characterised by relapses and remissions. It can be treatment refractory (resistant), with a heterogeneous clinical course.¹⁻³ When indolent, some patients may not require treatment for prolonged periods, while others may develop more aggressive forms that are refractory to standard treatment options.³ The EAG notes that the CS includes a population that is relapsed, progressive or refractory. The EAG clinical experts highlight that “progressive” implies disease worsening despite treatment and can also be considered refractory; “refractory” can also include stable disease (not progressing). “Relapse” refers to disease returning after a response. Therefore, relapsed or refractory are used by the EAG in this report, unless otherwise stated.

The CS (section 1.3.2 and 1.3.7) states that “*by 4L+ stage, R/R FL is no longer considered an indolent disease but more akin to end of life disease with limited treatment options.*” The EAG notes that this statement lacks citation. The CS notes that by the 4L+ of treatment, patients with R/R FL have a median overall survival of less than 12 months, based on observational data.^{2, 4}

FL grading and staging

The company states that FL is graded according to the 2022 WHO classification into four distinct grades based on centroblast count per high-power field (CS section 1.3.5). The EAG notes that the updated WHO-HAEM5 classification makes grading of FL optional,⁵ due to concerns about poor reproducibility, lack of standardised methodology, and limited clinical significance in distinguishing between grades 1, 2, and 3A.

CS section 1.3.5.2 states that the Lugano classification system (using fluorodeoxyglucose–positron emission tomography scans and an adaptation of the Ann Harbor staging system) is used to determine the staging of FL and provides additional information (CS Table 4). The EAG notes that no citation is provided.

Prognosis

Both the Follicular Lymphoma International Prognostic Index (FLIPI) developed in 2004⁶ and FLIPI2 (2009)⁷ are prognostic tools used in the assessment of FL.⁸ While FLIPI is based on five clinical factors: age >60, Ann Arbor stage III/IV, haemoglobin <120 g/L, involvement of >4 nodal sites and elevated serum lactate dehydrogenase (LDH), FLIPI2 retains age and haemoglobin but replaces LDH with beta-2 microglobulin (B2M) - a more specific marker of tumour burden - and adds bone marrow involvement and nodal mass >6 cm. The CS (CS section 1.3.5.3), highlights that both are used to inform clinical prognosis but not guide treatment. The EAG clinical experts agree that some prognostic factors such as bone marrow involvement are not routinely used, therefore FLIPI is the most currently used tool in UK clinical practice.

Response criteria in FL is commonly assessed using the Lugano classification system, which includes the Lymphoma Response to Immunomodulatory Therapy Criteria (LYRIC) developed specifically to evaluate responses to immune-based

treatments.⁹ These criteria define complete response, partial response, and progressive disease based on imaging results such as PET/CT scans and changes in lesion size (CS Table 5). The company's EPCORE NHL-1 study,¹⁰ applies both the Lugano and LYRIC criteria to evaluate these treatment outcomes, see Table 5 for further details.

Burden of FL

CS section B.1.3.3 addresses the HRQoL burden of FL and states that quality of life declines in comparison with the UK general population.¹¹ However, the cited reference provides population norms only and does not include a direct comparison with FL patients. The EAG notes that the three studies cited by the company in section B.1.3.3¹²⁻¹⁴ do not specifically report on the burden on R/R FL patients. For example, the study by Cheung 2009¹² evaluates work productivity among a mixed cohort of indolent NHL patients at different stages, including those with R/R FL, but does not report results for this subgroup. Similarly, Major 2022¹³ reports on HRQoL in newly diagnosed patients with indolent NHL, including FL, but excludes patients with R/R disease. The study by Lee 2013¹⁴ provides HRQoL data across all cancer types, with 84% of patients diagnosed with stomach or lung cancer; the remaining cancer types, including FL, are not specified. The company describes a study they conducted into patient experience of living with FL.¹⁵ While this qualitative study addresses the emotional burden experienced by patients at 1L to 3L of treatment, it is based on interviews with a small number of patients / caregivers (n=13), 3 of whom were from the UK and only one patient was at 3L. Furthermore, no standardised instruments were used to assess or report emotional burden.

2.2.2 Position of the technology

The company describes treatment pathways for FL in CS section 1.3.6 and presents an overview of current treatment options in CS Figure 1 (not reproduced here). Apart from a few exceptions the EAG clinical experts confirm that the representation is reasonable. Symptomatic high tumour burden stage III and IV (advanced-stage) FL follows British Society of Haematology (BSH) treatment guidelines⁸ with an anti-CD20 antibody treatment (rituximab or obinutuzumab) in combination with chemotherapy (cyclophosphamide, doxorubicin, vincristine and prednisolone

[CHOP], or cyclophosphamide, vincristine and prednisolone [CVP], or bendamustine). The EAG clinical advisors agree with the company that there is no standardised treatment pathway for relapsed / refractory FL at later lines of treatment. Treatments used will depend on prior treatments used, responses to those prior treatments as well as clinical judgement about fitness. For some, a repeat rituximab with chemotherapy option is used as per the BSH guidelines,⁸ but other treatments include rituximab with an alternative chemotherapy, lenalidomide with rituximab (R2) or other regimens such as bendamustine, gemcitabine, cisplatin with different centres using more or less intensive regimens. Obinutuzumab in combination with other therapies is rarely used at later treatment lines in the UK.

As there is no standard of care for the treatment of 4L+ FL, currently used treatments are aimed at controlling the disease rather than achieving remission. Although the EAG experts agree with the CS that there is an unmet need at 4L+, unlike the company experts, the EAG experts consider that there is a greater unmet need at 3L+ and that it is desirable to consider using epcoritamab at 3L+. They suggest that as most patients will have already received rituximab and chemotherapy and then rituximab with lenalidomide, the choice of the next line of therapy is difficult and that it would not be desirable to give bendamustine later because of how it affects T-cell function; it would therefore be of benefit for patients to have the option of epcoritamab at third line.

Best supportive care (BSC) was not considered an appropriate comparator by the company because they expect that BSC would be for those not fit enough for an active intervention. The EAG clinical experts confirmed that fitness would be based on performance status. The EAG clinical experts considered that some people at 4L+ who would not be fit enough for chemotherapy would be eligible for epcoritamab treatment instead of receiving BSC and that therefore, the exclusion of BSC as a comparator is not appropriate.

Current NICE recommendations for FL are presented in CS Table 7. The EAG clinical experts agree that it is unlikely that any of these interventions would be used in 4L+ or 3L+ as they would have already been used as second-line in the majority of cases.

The CS outlines their case for the unmet need at 4L+ in Section 1.3.7. The EAG experts agree that FL at later stages is often resistant to conventional treatment and that the CS estimates of median overall survival (OS) at 4L+ of less than a year (■■■■ months) and median progression free survival (PFS) of ■■■■ months is reasonable.⁴

The CS reports that there are limited treatment options at 4L+. The CS also reports that existing chemotherapy-based treatments do not fully address the immune dysfunction associated with FL and have a number of toxicities which mean they're not suitable to be repeated. The CS cites a systematic review of cardiovascular events at first line CHOP or R-CHOP chemotherapy in NHL, rather than FL specifically, where the review identified that cardiac dysfunction is reported in more than 10% of individuals post-chemotherapy. The EAG clinical experts agree with these issues but note that they are not specific to 4L+ FL.

CS Table 2 reports details of epcoritamab. Epcoritamab is a humanised IgG1-bispecific antibody that binds the B-cell antigen CD20 and T-cell antigen CD3, encouraging destruction of abnormal FL cells. The marketing authorisation is for adult patients with R/R FL after two or more lines of systemic therapy. Epcoritamab is administered subcutaneously (sc), whereas other treatments are administered intravenously. The company has submitted a new indication application to the UK Medicines and Healthcare Products Regulatory Agency (MHRA) and a decision is expected in ■■■■. The epcoritamab dose is increased during the first 4-week cycle to 48 mg from 0.16 mg on day 1, 0.8 mg on day 8, 3 mg on day 15 and 48 mg on day 22.

2.3 Critique of company's definition of decision problem

The decision problem in the company's submission has some differences to the final NICE scope. The population in the company's decision problem is narrower than the NICE scope and the UK marketing authorisation and the EAG considers there to be an unmet need in the wider population, in line with the NICE scope, see Table 3 for more discussion. The comparator in the company's decision problem is also narrower than the NICE scope, which the EAG considers is appropriate.

Table 3: Summary of decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
Population	Adults with relapsed or refractory follicular lymphoma (FL) after 2 or more systemic treatments	Adults with relapsed or refractory FL after 3 or more systemic treatments	The company submission focuses on the patient population with the greatest clinical unmet need and where there are limited treatment options.	The company focuses on the population with FL after 3 or more treatments (4L+). On advice from the clinical experts the EAG considers that the greatest unmet need, where optimised treatment options are required, is at 3L+. This is in line with the NICE scope and UK marketing authorisation for epcoritamab. While the clinical evidence submitted by the company is focused on their desired population, 4L+, the company also presents clinical effectiveness evidence for epcoritamab at 3L+ and the EAG has reported this evidence alongside the 4L+. Generalisability of the study to UK clinical practice is difficult to fully assess, in part owing to the small sample size, however, the EAG clinical experts did not have any major concerns with representativeness, this is discussed more in Section 3.6
Intervention	Epcoritamab	Epcoritamab	N/A	The intervention matches the NICE scope. Epcoritamab is a humanised IgG1-bispecific antibody and has UK marketing authorisation for the treatment of

				relapsed or refractory diffuse large B-cell lymphoma (DLBCL), with an application for FL submitted to the MHRA. Epcoritamab is given by subcutaneous injection at 48 mg after a dose escalation during the first 4-week cycle.
Comparator(s)	Established clinical management without epcoritamab. Treatment choice will depend on previous treatments, and how effective those treatments were. • Lenalidomide with rituximab • Obinutuzumab with bendamustine followed by obinutuzumab maintenance • Rituximab monotherapy • Rituximab with chemotherapy • Best supportive care	The comparators considered in this submission: Current 4L+ care as a basket of rituximab-based chemotherapy, chemotherapy, lenalidomide with rituximab, and other immune-based regimens	Based on consultation with UK clinical experts, the consensus is that there is no standard of care for relapsed/refractory FL 4L+. ¹⁶ Treatment is individualised. Therefore, the comparator treatment basket considered within this submission aligns with and reflects the lack of any specific standard of care treatment for patients in current UK clinical practice.	The EAG clinical advisers agree with the company's justification that the basket of care is an appropriate comparator for 4L+ and that the exclusion of other comparators in the NICE scope is appropriate with the exception of BSC (discussed above). The basket of care is also appropriate as a comparator at 3L+ but other comparators may be relevant at that line.

Outcomes	The outcome measures to be considered include: • Overall survival • Progression-free survival • Response rates • Adverse effects of treatment • Health-related quality of life.	The outcomes measure to be considered include: • Overall survival • Progression-free survival • Response rates (ORR, CR, PR) • Adverse effects of treatment • Time to treatment discontinuation • Health-related quality of life	All outcomes requested in the final scope are presented, with additional outcomes reported that are important to demonstrate the benefits of epcoritamab.	The outcomes in the CS match the outcomes in the NICE scope and these are appropriate to the assessment of epcoritamab for FL, although there were limited results for health-related quality of life reported. Additional outcomes are also reported as indicated by the company.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal	As per NICE scope	N/A	Follows NICE approach

	Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability and cost of biosimilar and generic products should be taken into account.			

3 CLINICAL EFFECTIVENESS

3.1 *Critique of the methods of review(s)*

The company conducted an SLR to evaluate the efficacy and safety of treatments for adult patients with 3L+ and 4L+ relapsed/refractory follicular lymphoma (R/R FL), reported in CS Appendix B.

3.1.1 Search strategies

Searches were originally undertaken in April 2023, with updates in March and November 2024. The EAG ran targeted searches for any studies relevant to the NICE scope that may have been added to databases since November 2024; this identified no additional, relevant studies. An appropriate selection of bibliographic databases, recent conference proceedings and clinical trials registries was searched. Reference lists of previous SLRs, pooled analyses and meta-analyses were also checked (CS Appendix B, Table 13), although reference lists of included studies do not appear to have been checked for additional studies. One further included publication was found via 'Supplementary evidence publications included for data extraction'; it is not clear what this means and the company's response to Clarification C12 is also unclear.

The database search strategies (reported in Appendix B, Tables 1-4 and Clarification C8 Appendix, Tables 8-1 to 8-10) combine terms for relapsed/refractory or 2L+ follicular lymphoma with interventions of interest and study type filters for randomised controlled trials (RCTs) and non-randomised studies. The EAG considers that since both interventional and observational studies were to be included in the review, the search strategy would have been more comprehensive had it not included study type filters, perhaps only excluding specific unwanted study or publication types such as case reports and letters (Appendix B, Table 13).

Publication date limits have been used in update search strategies to exclude results published before the date of the previous search. This is not best practice and risks missing relevant results, as publications are not added to Embase/Medline as soon as they are published. More appropriate date fields such as "date created" or "date

delivered” can be used for a comprehensive search. Additional limitations affecting the sensitivity of the search strategies include missing Emtree or MeSH headings for the relapsed/refractory concept (‘refractory cancer’, ‘cancer recurrence’, ‘salvage therapy’, ‘recurrence’), not including trade names nor alternative names for drug interventions, not using the drug trade name field in Embase, and not searching the keywords field (using title and abstract fields only for free text searches).

The company’s searches were for FL, therefore did not identify an epcoritamab study that reported results for of the LBCL group (Thieblemont 2024).¹⁷ The EAG considered this publication useful for reporting of adverse events (see section 3.2.7).

3.1.2 SLR methods

The company conducted the SLR from a global perspective and included comparators that are not relevant to the NICE decision problem. The population specified by the eligibility criteria (CS Appendix Table 13) is wider than both the UK marketing authorisation (adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy) and the population defined by the company’s decision problem (after 3 or more systemic treatments). The reporting of the results of the SLR is not clear, with a number of errors acknowledged by the company at clarification (Clarifications C5, C6, C11). In addition, full citations of the 490 excluded reports listed in CS Appendix B.7 and details of 238 additional publications subsequently excluded for not reporting 3L+ data were not provided with the initial submission (Clarifications C4 and C3, respectively).

Searches of clinical trial registries were undertaken. However, the methods stated that results were not extracted from studies reported only in clinical trial registries, which is a potential source of publication bias. The CS does not report details of relevant studies from clinical trial registries, but the company confirmed in Clarification C13 that there were no additional trials identified.

The company excluded conference abstracts if data were published in a more recent abstract or in a peer-reviewed publication. This is reasonable, but it is not clear from

the reasons for exclusion what the linked publication was for abstracts excluded for ‘study design’, making checking difficult.

Although the company included 54 studies reported in 107 publications (Clarification C5), only 38 studies are discussed in Appendix B.2 and no results for these 38 studies are reported. Most of these 38 studies assessed interventions that are not relevant to this appraisal. It is not clear why the CS omits the other 16 studies.

The EAG has checked all included and excluded publications lists, identified any studies with relevant interventions and checked for 3L+ and 4L+ data. There were a number of studies that were relevant to the decision problem (Table 4), but the EAG agrees with the company that none were appropriate for use in the MAIC for the 4L+ population. No studies with BSC were identified.

If the 3L+ population were to be considered, the following studies should be re-assessed:

Coiffier 2011¹⁸

Salles 2022¹⁹

Hao 2023²⁰

Wästerlid 2024²¹

Johnson 2024²²

Johnson 2025²³

Vitolo 2025²⁴

Table 4: Summary of SLR methods and EAG assessment of robustness

Systematic review step	EAG assessment of robustness of methods
Searches	There are several limitations to the search strategies which mean that relevant studies may have been missed.
Inclusion criteria CS Appendix B section B.1.6 and Table 13	The inclusion criteria were wider than appropriate for the decision problem, so many of the studies summarised in Appendix B.2 are not relevant.

Screening CS Appendix B.1.7	Appropriate: the publications were screened by two reviewers, with conflicts adjudicated by a third reviewer (Clarification C2).
Selection of included studies CS Appendix B.1.7	Although not clearly stated, full texts were screened in the same way as title and abstracts (Clarification C2). In response to Clarification C5, the company acknowledged errors in reporting of outcomes from the SLR in Appendix B.2; these errors are also displayed in PRISMA flow diagram in Appendix Figure 1. The company's SLR included 54 studies reported in 107 publications. However, only 38 of these are mentioned in the SLR; three of these are '<i>other drugs</i>' that aren't named or referenced. No results are reported for any of the studies included in the SLR. The EAG has checked all 107 included publications, and considers that most of the included studies have interventions are not relevant to this appraisal. Of those with relevant interventions Coiffier 2011¹⁸ may be useful if the 3L+ population is considered. The EAG has checked the list of publications excluded at the full text stage, and five were considered potentially relevant by the EAG. The company considered three of these further in section B.2.12.1.1 of the main submission (Salles 2022¹⁹ excluded on population; Casulo 2022,²⁵ excluded on Intervention; Ghione 2023,²⁶ excluded on intervention). The EAG considers the company's justification for excluding these studies from the MAIC as appropriate, however Salles 2022¹⁹ may be useful if the 3L+ population is to be considered. The other two studies identified from excluded studies list (Hao 2023²⁰ and Wästerlid 2024²¹) may also be useful for the 3L+ population. Patients receiving second or later line of therapy were initially included in the SLR. An additional step was undertaken to

	only include studies reporting data on patients receiving third-line treatments or above. The company confirmed this was undertaken by two reviewers with a third consulted if needed (Clarification C3). The company did not initially provide details of the 238 studies not reporting 3L+ data, but provided these in response to Clarification C3. The company also confirmed that the full text publications and any supplementary material were checked for relevant data. The EAG has checked these 238 publications and agree none was relevant.
Data extraction CS Appendix B.1.8	Appropriate: One researcher extracted the data, which was checked for accuracy and completeness by a second reviewer. In addition, the project manager quality assessed a random 10% of all articles extracted.
Tools for quality assessment CS Appendix B.5	A modified Downs and Black checklist was used for non-randomised studies, and a brief assessment is presented for the EPCORE NHL-1 study in CS Table 15. A full checklist was provided in response to Clarification C1. A narrative overview summarising other included studies was given in CS Appendix B.5, but results for individual studies were not provided. The CRD checklist was applied to RCTs, none were relevant to this appraisal.
Evidence synthesis	The CS provides a narrative description and summary tables of the key trial, EPCORE NHL-1. None of the studies identified by the SLR were considered by the company to be appropriate for use in an ITC. The EAG agrees with this. A narrative review of studies meeting eligibility criteria that are broader than relevant to the current appraisal is presented in CS Appendix B.2. However, this includes interventions that are not relevant to the decision problem and does not report any results.

3.2 Critique of trials of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)

The study providing safety and efficacy information for this indication of epcoritamab is EPCORE NHL-1 (NCT 03625037).

3.2.1 EPCORE NHL-1 study design

The EAG summary of the key characteristics of the EPCORE NHL-1 study, based on the company submitted information, is summarised in Table 5. The EAG has summarised the relevant parts, cohorts and subgroups of EPCORE NHL-1 in Table Table 6 and the data-cuts and sources of information in Table 7.

Table 5 combines data obtained and checked by the EAG from the CS and the available CSRs, NCT record,²⁷ company protocol version 14, the publication relevant to the EPCORE study¹⁰ and the abbreviated dataset provided at clarifications (A4).

EPCORE NHL-1, is an ongoing open label single arm phase 2 study, conducted in US, Australia, Asia and Europe to evaluate the safety and efficacy of epcoritamab in relapsed/refractory patients with B-cell lymphomas (diffuse large b-cell lymphoma: DLBCL; high-grade b-cell lymphoma: HGBCL; primary mediastinal b-cell lymphoma: PMBCL; follicular lymphoma, grade 3b: FL grade 3B; marginal zone lymphoma: MZL; small lymphocytic lymphoma: SLL and mantle cell lymphoma: MCL). The subgroup of relevance to the decision problem in this submission is patients with FL grades 1 to 3A. Eligible patients are ≥ 18 years old, who were relapsed, progressive and/or refractory to at least two prior lines of treatment (including anti-CD20 monoclonal antibody), having exhausted or are ineligible for standard treatment options and have an ECOG PS score 0 – 2.

The study consisted of 3 parts; an initial dose-escalation part which is not applicable to the decision problem; a dose expansion part and a dose-optimisation part which are the focus of this submission. The optimisation part of EPCORE NHL-1 had two arms, arm A (as shown in CS section 2.2, Table 9) which is relevant to this

submission while arm B (n=6) was irrelevant due to a difference in the step-up dose (6mg at day 15) from that in the anticipated licenced escalation.

Epcoritamab was administered subcutaneously per cycle (1 cycle was equivalent to 28 days). Participants received epcoritamab subcutaneously in 4-week cycles (i.e., 28 days) at varying doses as follows:

- Cycle 1: dose escalation, Day 1: 0.16 mg, Day 8: 0.8 mg, Day 15: 48 mg (Dose Expansion Part) or Cycle 1 Day 1: 0.16 mg, Day 8: 0.8 mg, Day 15: 3 mg, Day 22: 48 mg (Dose Optimisation Part)
- Cycle 2-3: Days 1, 8, 15, and 22 (once weekly) 48 mg
- Cycle 4-9: Days 1 and 15 (every 2 weeks) 48mg
- Cycles 10 to progressive disease (PD), unacceptable toxicity, or end of trial: Day 1 (every 4 weeks) 48 mg

The EAG notes a difference in the dose escalation between the expansion part (which informs the main evidence of this submission) and the optimisation part (and anticipated licensed escalation), see Table 5. In the latter, an additional dose of 3.0 mg at day 15 is included and the 48 mg dose commenced from day 22. In response to clarification question A10, the company explained the rationale for the difference and agreed that the expansion part did not include the 3 mg step used in the optimisation part and anticipated licenced escalation which is to improve tolerability. The company report that pharmacokinetic outcomes are very similar and that the 3-step regimen does not undermine the efficacy or safety data. The EAG clinical experts did not consider the different dosing escalations to have any bearing on clinical, or safety results seen.

The CS focuses primarily on the 4L+ subgroup. Data pertaining to the 3L+ subgroup are presented separately in CS Appendix M, Table 83 for completeness. As detailed in Section 1.3, the 3L+ population is consistent with the NICE scope.

The clinical data in the CS are based on the most recent data cut of [REDACTED], (median follow-up [REDACTED] months) in the expansion part and 8 January 2024 (median follow up 5.7 months) in the optimisation part. The expansion part primary endpoint of relevance to the decision problem was overall response rate (ORR) per Lugano

criteria and assessed by independent review committee (IRC), with secondary endpoints including response rates, PFS, OS, safety and HRQoL, see Table 5 for further details. Primary endpoints in the optimisation part included Cytokine release syndrome (CRS) events and safety, while secondary endpoints were similar to those of the expansion part but excluded HRQoL, Table 5.

Table 5: Summary of included epcoritamab study (characteristics)

EPCORE NHL-1		Section(s) of CS of relevance or other source
Study details	EPCORE NHL-1 (NCT03625037) US, Australia, Canada, Denmark, Finland, France, Germany, Italy, Netherlands, Poland, Spain, Sweden, UK, Singapore, Republic of Korea Years of recruitment: Not reported Data cut off relevance: Expansion Part: [REDACTED] (median follow-up: [REDACTED]) Dose optimisation part: 8th January 2024 (median follow-up 5.7 months)	CS Document B, section 2.2, Table 8 and 9 Company study protocol v 14²⁸ Company CSR Clinicaltrials.gov²⁷ Linton 2024¹⁰
Study design	Open label phase 1/2, single arm study The study consists of 3 parts: • A dose-escalation part [Phase 1, first-in-human (FIH)] not reported here • An expansion part (Phase 2a) • A dose-optimisation part (OPT) (Phase 2a) The trial included participants with other B-cell lymphoma's (DLBCL, HGBCL, PMBCL, FL grade 3B, MZL, SLL and MCL) as well as FL, the subgroup of relevance to the decision problem.	CS Document B, section 2.2, Table 8 and 9, Company CSR, Linton 2024¹⁰
Intervention	Epcoritamab subcutaneous injection 48 mg once weekly. The dose expansion part treatment was administered in 4-week cycles and commenced with a dose escalation in cycle 1 at 0.16 mg on day 1, 0.80 mg on day 8, 48 mg on day 15. In the dose optimisation part, there was another intermediate dose of 3.0 mg at day 15 and the 48 mg dose commenced from day 22. This is the anticipated licensed dose escalation (see CS Table 2). After 3 cycles treatment was administered once every two weeks for cycles 4 to 9, and once every four weeks from cycle 10 until unacceptable toxicity, disease progression, or withdrawal of consent.	CS Document B, section 3.2.3.1, Table 9. Company study protocol v 14.0, Company CSR, Linton 2024¹⁰
Sample size	Dose expansion part 3L+: N=128 Dose expansion part 4L+: N=81 Dose optimisation part 3L+: N=86 Dose optimisation part 4L+: N=41	CS Document B, section 2.5, Figure 6

Population	Key inclusion criteria: • Aged ≥ 18 years • Histologically confirmed FL grades 1 – 3A (WHO criterion) • Relapsed, progressive (clarification q A16) and/or refractory following treatment with anti-CD20 monoclonal antibody • One measurable disease site based on CT/MRI • Exhausted or ineligible for standard care • ECOG PS 0-2 A complete list of the population eligibility is reported in CS Section 2.5, Table 10	CS Document B, section 2.5, Table 10, Company CSR, Linton 2024 ¹⁰
Subgroup of relevance to the decision problem	Data of relevance to the NICE scope: FL patients at 3L+ Data of relevance to the company decision problem: FL at 4L+	CS Document B, section 2.2 and 2.5 Company CSR
Outcomes	The outcomes of relevance to the decision problem are listed below: Expansion phase Primary endpoint • ORR: determined by LUGANO criteria and assessed by IRC, defined as: the proportion of patients who reached a best overall response of partial response or complete response at any time. Secondary endpoint • ORR: As per definition above, determined as per the LYRIC criteria • Complete response rate (CRR): Proportion of patients with BOR of CR • PFS^a: Time from day 1 of cycle 1 to the date of PD or death, due to any cause, whichever comes first. • OS^a: Time from day 1 of cycle 1 to death from any cause • Safety • FACT-Lym and EQ-5D-3L: Changes in lymphoma symptoms as measured by the Functional Assessment of Cancer Therapy - Lymphoma and EQ-5D-3L Optimisation phase Primary endpoint analysis • Cytokine measures: Rate of ≥ 2 grade CRS event and all grade CRS event from first dose through 7 days of administration of the second dose. • Safety and AEs Secondary endpoints	CS Document B, section 2.6, Table 13, Company study protocol v 14.0, Linton 2024 ¹⁰

	• Cytokine measures: Rate of ≥ 2 grade CRS event and all grade CRS event following first full dose and overall • Safety and AEs: Including laboratory parameters [biochemistry, haematology including immunophenotyping for absolute T-cell and B-cell counts as well as T-cell activation and exhaustion markers], hospitalizations, and PK parameters (clearance, volume of distribution, Cmax, Tmax, trough concentrations, and half-life) and incidence of anti-drug antibodies (ADAs) to GEN3013 • ORR • CR • DOR • DOCR • PFS • OS	

DLBCL: Diffuse Large B-Cell Lymphoma, HGBCL: High-Grade B-Cell Lymphoma, PMBCL: Primary Mediastinal B-Cell Lymphoma, FL grade 3B: Follicular Lymphoma Grade 3B, MZL: Marginal Zone Lymphoma, SLL: Small Lymphocytic Lymphoma, MCL: Mantle Cell Lymphoma C1 – Opt: Cohort 1 Optimisation, 3L+: Third line or later, 4L+: Fourth line or later, ORR: objective response rate, CRR: complete response rate, PFS: Progression free survival, OS: Overall survival, TTNT: Time to next anti-lymphoma, BOR: Best overall response to treatment, CR: complete response, CRi: complete response with incomplete bone marrow recovery, OD: Progressive disease, ECOG PS: Eastern Cooperative Oncology Group performance status, AEs: adverse events, ADA: Anti-drug antibody, CRS: Cytokine release symptoms, MRD: Minimal residual disease, PK: Pharmacokinetic parameters, Cmax: Maximum concentration (of a drug in blood), Tmax: Time to maximum concentration, FIH: First in human, FACT-Lym: Functional Assessment of Cancer Therapy – Lymphoma, CT: Computed tomography, EQ-5D-3L: EuroQol 5 Dimensions 3 Level^a used in economic model

Table 6: Summary of EPCORE NHL-1

	Dose expansion part	Dose optimisation part
Dose	Cycle 1 D1: 0.16 mg, D8: 0.8 mg, D15: 48 mg	Cycle 1 D1: 0.16 mg, D8: 0.8 mg, D15 3 mg, D22: 48 mg
Cohorts	Three cohorts of patients with NHL: LBCL iNHL (n=155) MCL	Three cohorts of patients with: FL grades 1-3A DLBCL MCL
Relevant cohorts	iNHL cohort includes: 3L+ FL 1-3A (n=128) MZL (n=23) SSL (n=4)	3L+ FL grades 1-3A includes: Arm A (n=86) Arm B (n=6) different step-up dose
Further subgroups	3L+ (n=128): 3L-only (n=47) not reported 4L+ (n=81)	3L+ (n=86): 3L-only (n=45) not reported 4L+ (n=41)

Source: Adapted from CS Table 9. Bold indicates information relevant to appraisal

Table 7: Data-cuts and sources of information of EPCORE NHL-1 presented in the EAG report

the EAS report

	Data-cut	Median follow-up, months	Source of information			
			CS	CSR	Clarification A4 data tables	Publication ¹⁰
Dose expansion part						
3L+ (n=128)	21 April 2023	17.4	No	Yes	No	Yes
3L+ (n=128)			Yes	No	No	No
4L+ (n=81)			Yes	No	Yes	No
Dose optimisation part						
3L+ (n=86) ^a	8 Jan 2024	5.7	Yes	Yes	No	No
4L+ (n=41)	8 Jan 2024	5.7	Yes	No	Yes	No

3.2.2 Baseline characteristics

The EPCORE NHL-1 trial was a single arm study divided into three parts, two of which are relevant to the efficacy of epcoritamab; the CS presented data for two different subgroups from each part as discussed earlier (EAG report section 3.2.1). In this section, the EAG summarises the baseline characteristics of the 4L+ and 3L+ subgroups, from both the expansion and optimisation parts of EPCORE NHL-1. Data for the 4L+ subgroup of the expansion and optimisation parts were obtained from the CS, Section 2.5.1 – 2.5.2.2, Table 11 and Section 2.14.2, Table 39, respectively. Additional data for these subgroups was also available from CS Appendix M. The EAG was unable to validate these data from any publications or the submitted CSR and requested documents for the 4L+ subgroups at clarification (Clarification question A4). In their response, the company stated that there were no publications or CSR available for the 4L+ cohorts and instead provided an abbreviated dataset. The EAG was able to validate these data for the 4L+ expansion phase and notes that for the optimisation phase, some of these data were only in a summary document provided by the company. Data for the 3L+ expansion and optimisation cohorts were obtained from CS Appendix M and validated with CSRs, and the publication.¹⁰ An overview of the patient characteristics is summarised in Table 8 and key points discussed below.

The EPCORE NHL-1 study subgroups submitted in the CS were the expansion part 4L+ (n = 81) and 3L+ (n = 128), and the optimisation part 4L+ (n = 41) and 3L+ (n =

86). These are not mutually exclusive groups, the 4L+ groups are subsets of the respective 3L+ groups. The EAG summarises key prognostic characteristics from across these subgroups to consider representativeness of the participant cohorts, rather than for any comparison. The mean age of participants ranged from 62.8 to 65.5 years, indicating a predominantly older population consistent with the typical age profile of FL.²⁹ The expansion part subgroups showed a higher proportion of male participants, which aligns with the known epidemiological pattern of FL in the UK (i.e., male-to-female ratio ~1.4:1).²⁹ In contrast, the optimisation cohorts 4L+ group showed more balanced sex distribution. Most patients included had ECOG PS 0 – 1 across all cohorts, indicating a generally fit population. A small proportion of patients in the expansion subgroups had an ECOG PS of 2 (3.7% and 5.5% for the 4L+ and 3L+ subgroups respectively) and none in the optimisation subgroups had a PS above 1, see Table 8. Minor differences were also observed across cohorts in histological grade, FLIPI score, and refractory status, these are summarised in Table 8.

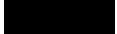
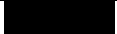
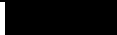
The EAG notes that patients were heavily pre-treated, particularly in the 4L+ groups, with 49.4% of patients receiving ≥4 prior lines of therapy (expansion 4L+) and 41.5% in the optimisation phase. Some patients had received later-line treatments such as lenalidomide (up to ■■■). Approximately ■■■ of patients underwent stem cell transplant and fewer than 10% of patients in each subgroup had received prior CAR-T. As the EPCORE NHL-1 protocol excludes those with prior CAR-T therapy within 30 days of enrolment, the EAG asked the company for more details about the participants who had received prior CAR-T (clarification A14). The company response reports on the participants from the 4L+ expansion subgroup (n=■; ■■■) and noted that these individuals had relapsed and were considered high-risk. As such, no long-term benefit from prior CAR-T was expected.

To ascertain the generalisability of the EPCORE NHL-1 trial to the UK population, the EAG requested additional information on the UK participant sample size across all cohorts including baseline characteristics data specific to the expansion 4L+ (n=81). In clarification question A11, the company stated that a small UK sample size population of ■■■ patients were enrolled in the 4L+ expansion subgroup. Baseline characteristics for the UK sample were provided (clarification question A11,

Table 2, not reproduced here). The company reports that compared to the overall 4L+ cohort, the UK population was younger (mean age [REDACTED] years), [REDACTED] of white race and predominantly male ([REDACTED]). In the CS document B, section 2.15.2, the company suggested that the EPCORE NHL-1 trial was generalisable to UK clinical practice in that a high proportion of patients were from European countries of which [REDACTED] were from the UK. However, the EAG consider that [REDACTED] UK patients represent a [REDACTED]. The company's clinical experts considered that the EPCORE NHL-1 study could be generalised to the UK. They also considered that the participants presented with higher-risk risk features than seen in real world populations.¹⁶ The EAG clinical experts generally agreed that the EPCORE NHL-1 trial was generalisable to UK clinical practice, discussed in more detail in Section 3.6.

Table 8: summary baseline characteristics of included epcoritamab study

Characteristic	Expansion phase, 4L+ (N = 81)^a	Expansion phase 3L+ (N = 128)^{b, f}	Optimisation phase 4L+ (N = 41)^a	Optimisation 3L+ (N = 86)^f
Age, years				
Mean (SD)	64.8 (11.06)	63.2 (11.20)	65.5 (8.99)	62.8 (10.98)
Median (min, max)	66 (39, 84)	65 (39, 84)	66 (46, 81)	64 (55, 71)
Male Sex, n (%)	53 (65.4)	79 (61.7)	20 (48.8)	49 (57)
Race, n (%)				
White	51 (63)	77 (60.2)	31 (75.6)	64 (74.4)
Black or African American	0	0	0	1 (1.2)
Asian	3 (3.7)	7 (5.5)	1 (2.4)	2 (2.3)
Other	0	2 (1.6)	0	0
Not reported	27 (33.3)	42 (32.8)	9 (22)	19 (22.1)
ECOG PS, n (%)				
0	40 (49.4)	70 (54.7)	25 (61)	52 (60)
1	38 (46.9)	51 (39.8)	16 (39)	34 (40)
2	3 (3.7)	7 (5.5)	0	0
Histological grade, n (%)				
1	9 (11.1)	16 (12.5)	11 (26.8)	20 (23.3)
2	45 (55.6)	70 (54.7)	22 (53.7)	46 (53.5)
3A	27 (33.3)	41 (32)	6 (14.6)	17 (19.8)
Unknown	NA	NA	2 (4.9)	3 (3.5)
Not applicable	0	1 (0.8)	NR	0
FLIPI, n (%)				
0-1	11 (13.6)	17 (13.3)	5 (12.2)	11 (13)

2	13 (16)	31 (24.2)	10 (24.4)	31 (36)
≥3	57 (70.4)	78 (60.9)	26 (63.4)	44 (51)
Unknown	0	1 (0.8)	0	0
Not applicable	0	1 (0.8)	0	0
Time from initial diagnosis to first dose (years)				
Median (min, max)	0	6 (3, 11)		8 (5, 11)
Disease status, n (%)				
Refractory	62 (76.5)	88 (68.9)		49 (57)
Relapsed	19 (23.5)	40 (31.3)		37 (43)
Bulky disease, n (%)				
≤ 6 cm		95 (74)		69 (80)
> 6 cm		33 (26)		17 (20)
Prior lines of therapy, n (%)				
Median (min, max)	0	3 (2, 4) ^d		2 (2, 3) ^d
1 prior therapy	0	0		0
2 prior therapy	0	47 (37) ^d		45 (52) ^d
3 prior therapy	41 (50.6) ^c	41 (32) ^d		24 (28) ^d
≥4 prior therapies	40 (49.4%) ^c	40 (31) ^d		17 (20) ^d
Median (min, max) time from end of last-line anti-lymphoma therapy to first dose, months		5 (2 - 17) ^e		9 (3 - 28) ^e
Median (min, max) time from end of last anti-CD20 containing therapy until 1st dose, months		10 (3 - 22)		10 (4 - 32)
Prior therapy, n (%)				
Stem cell transplant	15 (18.5)		9 (22.0) ^h	
Radiotherapy	26 (32.1)		17 (41.5%) ^h	
CAR-T	6 (7.4)	6 (5)		6 (7)
Lenalidomide	NR	40 (31.3)		
Rituximab + Lenalidomide	25 (30.9)	27 (21.1)	NR	NR

NR: Not reported, ECOG, Eastern cooperative oncology group; FL, follicular lymphoma; FLIPI, follicular lymphoma international prognostic index.

^a The EAG verified this data with the abbreviated dataset provided at clarification question A4 and notes that this dataset was not the CSR

^b Among subjects with FL, all but one subject (99.2%) had FL Grade 1-3A at study entry. One subject was enrolled as FL but was found to have transformed DLBCL after study entry. This subject is included in the FL FAS.

^c Prior lines of therapy include anti lymphoma

^d Prior lines of therapy include Prior therapies: All including an anti-CD20 monoclonal antibody and an alkylating agent or lenalidomide

^e Data source¹⁰ states, "time from end of previous line of therapy to first dose of epcoritamab, months" and does not explicitly state if "anti lymphoma"

^f Data obtained from Linton et al (2024)¹⁰

^g Data obtained from 2024 data cut-off (DCO) Tabular (CS Appendix M – additional safety and efficacy data)

3.2.3 Risk of bias of EPCORE NHL-1

The company SLR reported that the Down and Black risk of bias checklist was applied to EPCORE NHL-1; however, this was not included in the CS. The company presented a table with risk of bias questions which was not referenced. Some of the questions are those used in the NICE methods guide³⁰ but there were also some additional questions. The EAG has undertaken an assessment with these same questions in Table 9 below. In response to clarification question C1, the company provided the full quality assessment of the EPCORE NHL-1 trial using the Down's and Black checklist. The EAG in Table 10, compares their responses to the Down's and Black checklist criteria with that of the company's assessment. Overall, the EAG has no major concerns on the EPCORE NHL-1 risk of bias. The EAG notes that, due to the study design (single-arm study), several items in the Down and Black checklist were not applicable, including randomisation, comparability between groups, and blinding.

There are some differences between the EAG and the company's assessments (Tables below). The EAG disagrees with the company's assertion that patient characteristics for those lost to follow-up were described. The EAG notes that characteristics of censored patients (e.g., those receiving new anti-lymphoma therapy or affected by COVID-related mortality) were not detailed, thus limiting ability to fully assess the impact of incomplete follow-up. Details of characteristics for COVID-censored patients were presented by the Company at Clarification Questions (Appendix 1) and were described in response to Question A25. The EAG also notes a difference between the dose escalation used in the expansion phase (efficacy data) and the licensed, optimised regimen. The company assessment of representativeness of the study population was 'unclear', whereas the EAG considered that the study population may not represent the entire population from which participants were recruited. For example, the company did not state the source population for recruited patients and while the CS stated the eligibility criteria, it did not describe how the patients were selected.

The EAG considered the data presented for the subgroups to be pre-specified and unlikely to be related to data dredging; it is interesting that the company assessment was unclear.

In addition, the EAG notes that p-values were not reported for patient-reported outcome data, despite before and after comparisons being presented.

Table 9: Company's quality assessment criteria of EPCORE NHL-1

	Company assessment	EAG assessment
What is the study design of this trial?	Single armed	Single armed
Was the study a prospective or a retrospective study?	Prospective	Prospective
In case of a case control study, were the groups similar at the outset of the study in terms of prognostic factors	N/A	N/A
Was the intervention used appropriately?	Yes, the dosing regimen in the trial reflects the expected dosing schedule for epcoritamab in its SmPC.	Yes However, the EAG notes a difference in the dose escalation between the expansion part (which informs the main evidence of this submission) and the optimisation part (and anticipated licensed escalation).
Were the outcomes measured in the study reliable?	Yes, the key outcomes of the trial are objective measures such as survival. Other key results such as response rates were determined by both independent review committees and the investigator.	Probably Yes All main outcomes were defined and stated apriori. In the expansion phase, ORR, TTR, DOR, CR, DOCR, PFS was assessed by an independent review committee (IRC) per Lugano criteria in full analysis set However, in the optimisation phase, ORR, CR, DOR, DOCR, PFS were assessed by investigator only which may introduce bias

Were the outcomes measured in the study valid?	Yes, the outcomes of the trial align with the decision problem and are clinically relevant measures to demonstrate the benefits of epcoritamab.	Yes The EAG agrees with the company's rationale
Was the statistical analysis conducted appropriately in the study?	Yes, the study was powered to provide statistically robust results	Yes The EAG agrees with the company's rationale
Was the quality of the reporting appropriate in the study?	Yes, all outcomes are reported in the clinical study report	Yes The EAG agrees with the company's rationale
Can the study results be generalised to routine practice?	Yes, more details are provided in Section 2.15.2	Probably Yes While the UK sample size was relatively small, the EAG clinical experts generally agree that the patient characteristics in the EPCORE NHL 1 study can be generalised to UK clinical practice

ORR: Objective Response Rate, TTR: Time to Response, DOR: Duration of Response, CR: Complete Response, DOCR: Duration of Complete Response, PFS: Progression-Free Survival, IRC: Independent Review Committee

Table 10: Down and Black critical appraisal for EPCORE NHL – 1 study

Description of criteria	Company Response [Requested at clarification, question C1]	EAG Response
Is the hypothesis/aim/objective of the study clearly described?	Yes	Yes
Are the main outcomes to be measured clearly described in the Introduction or Methods section?	Yes	Yes
Are the characteristics of the patients included in the study clearly described?	Yes	Yes
Are the interventions of interest clearly described?	Yes	Yes However, the EAG notes a difference in the dose escalation between the expansion phase (which informs the main evidence of this submission) and the optimisation phase (and anticipated licensed

		escalation). In the latter, an additional dose of 3.0 mg at day 15 and the 48 mg dose commenced from day 22 in the optimisation phase. Further details are reported in clarification question A10.
Are the distributions of principal confounders in each group of subjects to be compared clearly described?	N/A	Yes
Are the main findings of the study clearly described?	Yes	Yes
Does the study provide estimates of the random variability in the data for the main outcomes?	Yes	Yes
Have all important adverse events that may be a consequence of the intervention been reported?	Yes	Yes
Have the characteristics of patients lost to follow-up been described?	Yes	Probably No The characteristics of patients lost to follow-up (i.e., censored due to new anti-lymphoma therapy or other reasons) have not been described. In response to clarification questions A19 – A21, the company explain why censoring was applied and how it was handled methodologically, but they do not provide details on the profile or proportion of censored patients relative to the overall study population.
Have actual probability values been reported (e.g., 0.035 rather than <0.05) for the main outcomes except where the probability is less than 0.001?	No	No P- values were not reported for the main outcomes as there was no statistical testing (CS document B, section 2.6) However, the CS presents the before and after data on patient reported outcomes (PROMS). The EAG notes that none of these are reported with p-values both in CS, document B and CSR.
Were the subjects asked to participate in the study representative of the entire population from which they were recruited?	Unsure	No The company does not state the source population for the recruited patients. While the CS states the eligibility criteria, it does not describe how the patients were selected.
Were the staff, places, and facilities where the patients were treated,	Unsure	Unable to determine In response to clarification question

representative of the treatment the majority of patients receive?		A11, the company provided baseline characteristics on the UK sample size for the 4L+ expansion cohort (Clarification question A11, Table 2). No details of UK treatment centres were provided in the CS. Therefore, the EAG is unable to determine the representativeness of these centres for the wider UK population.
Was an attempt made to blind study subjects to the intervention they have received?	No	No As this is a single-arm study with no comparators, all subjects, staff and investigators were unblinded.
Was an attempt made to blind those measuring the main outcomes of the intervention?	No	No As this was a single arm study, none of the investigators were blinded in assessment of response. Further, some outcomes were assessed by the independent review committee. However, no information is provided regarding how these outcome decisions were made.
If any of the results of the study were based on “data dredging”, was this made clear?	Unsure	Yes The company did pre-specify line of therapy in their subgroup analyses which included prior anti lymphoma therapies at 2,3 and 4L+ (Company SAP). Therefore, the inclusion of the 4L+ data which is a subgroup of the EPCORE NHL 1 study was made clear
In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case control studies, is the time period between the intervention and outcome the same for cases and controls?	No	NA As this was a single arm study
Were the statistical tests used to assess the main outcomes appropriate?	Yes	NA No statistical tests were performed.
Was compliance with the intervention/s reliable?	Unsure	Unable to ascertain due to lack of information
Were the main outcome measures used accurate (valid and reliable)?	Yes	Probably Yes All main outcomes were defined and stated <i>a priori</i> . In the expansion phase, outcomes were assessed by IRC per Lugano criteria.

		In the optimisation phase, outcomes were assessed by investigator which may be a potential source of bias.
Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?	NA	NA Due to single arm study design
Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same time?	NA	NA
Were study subjects randomised to intervention groups?	NA	NA
Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?	NA	NA
Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?	Yes	Probably Yes Confounders were not prespecified in the EPCORE NHL-1 study protocol. However, the company submission states that clinical experts were consulted and that a preliminary investigation was conducted based on EPCORE NHL-1 data. Without clear pre-specification or detailed reporting of confounders in each group, the EAG is unable to fully ascertain the extent of potential confounding.
Were losses of patients to follow-up taken into account?	Unsure	Yes
Did the study have sufficient power to detect a clinically important effect where the probability value for a difference due to chance is less than 5%.	Yes	Yes

3.2.4 Patient disposition in EPCORE NHL-1

Patient disposition is reported for the 4L+ cohort in CS Table 12. The EAG had a few concerns regarding this table, and these were addressed by the company in Clarification responses A15, A16 and A17 (see Table 11 and footnotes for details). The main reason for treatment discontinuation was progressive disease [REDACTED], either by documented radiographic disease progression or symptomatic deterioration

without use of objective criteria (Clarification A15). In [REDACTED] of cases, adverse events were the reason for treatment discontinuation. [REDACTED] was the most common reason for trial discontinuation [REDACTED].

Details for the Expansion 3L+ cohort are presented in CS Appendix Table 66 and are summarised below. Discontinuation rates appear slightly lower in the 3L+ cohort compared with 4L+, with fewer discontinuing due to progressive disease [REDACTED], but this could be a spurious observation.

Patient disposition is not reported in the CS for the Optimisation 4L+ or 3L+ subgroups. Data were available in the CSR for the Optimisation 3L+ subgroup only and are presented in Table 11. Treatment discontinuation and study discontinuation rates are lower in the Optimisation part than in the Expansion part, but this is likely due to the [REDACTED] follow-up ([REDACTED] months) for this ongoing study.

Table 11: Patient disposition

	Expansion Part ^a		Optimisation Part ^e
	4L+ (N = 81)	3L+ (N = 128)	3L+ (N = 86)
Treatment discontinuation			
Ongoing trial treatment	[REDACTED]	[REDACTED]	[REDACTED]
Discontinued treatment	[REDACTED]	[REDACTED]	[REDACTED]
<i>Primary reason for study treatment discontinuation</i>			
Progressive disease ^b	[REDACTED]	[REDACTED]	[REDACTED]
Clinical Progression ^c	[REDACTED]	[REDACTED]	[REDACTED]
Disease progression according to response criteria	[REDACTED]	[REDACTED]	[REDACTED]
Adverse event	[REDACTED]	[REDACTED]	[REDACTED]
Death	[REDACTED]	[REDACTED]	[REDACTED]
Withdrawal of subject	[REDACTED]	[REDACTED]	[REDACTED]
Decision to proceed with transplant	[REDACTED]	[REDACTED]	[REDACTED]
Other ^d	[REDACTED]	[REDACTED]	[REDACTED]
Study discontinuation			
Patients remaining on trial	[REDACTED]	[REDACTED]	[REDACTED]
Discontinued from trial	[REDACTED]	[REDACTED]	[REDACTED]

<i>Primary reason for trial discontinuation</i>			
Death	████████	████████	████████
Lost to follow-up	█	████████	████████
Subject withdrew consent from trial	████████	████████	████████

Source: CS Table 12, Clarification A17, CS Appendix Table 66, CSR. ^a Data cut ██████████, ^b Progressive disease includes both clinical progression and documented radiographic disease progression; Clarification A17 notes a formatting error in CS Table 12 (corrected here) which could lead to double counting. ^c Clarification A15 states that in rare cases, the determination of clinical progression was based on symptomatic deterioration (i.e. without documented progression through the use of objective criteria). ^d Specific reasons are reported in Clarification A16 for Expansion 4L+ and in CS Appendix Table 66 for Expansion 3L+. ^e Data cut 08 Jan 2024.

3.2.5 Results

Overview of results

Key results from the EPCORE NHL-1 study are summarised in Table 12. These are presented for the expansion part and the optimisation part of EPCORE NHL-1. The CS focused on outcomes for the 4L+ subgroup; but as discussed in Section 2.3, the EAG has also considered outcomes for the 3L+ subgroup.

At clarifications (A4) the company confirmed that no CSR was available for the 4L+ data from the expansion or optimisation part. The company provided an unpublished document containing the formal tables, listings and figures for the key characteristics and outcomes for the 4L+ subpopulation which the EAG has used to validate data where possible. There are no published sources of the 4L+ subgroup analyses. For the 3L+ expansion part, the data cut presented by the CS is ██████████. The data cut in the submitted CSR is 21 April 2023, corresponding to the published data in Linton 2024.¹⁰ The EAG is therefore unable to validate the data for the 3L+ subgroup from the most recent data cut presented in the CS.

As the data for the main submission are from subgroup analyses which are not mutually exclusive groups, the EAG requested (clarification A5 and A8) summary efficacy data for the subgroup who only received third-line treatment (3L-only) from both parts of EPCORE NHL-1 for completeness. This would permit the EAG to consider any limitations in the data such as inconsistencies in the effects seen. The company declined to present these data only noting that data for the 3L+ population were presented, which includes the 3L-only subgroup. Although the EAG

summarises the 3L+ data, unfortunately this does not permit any consideration from the contrasting data to the 4L+ subgroup.

Results from the expansion part are from independent review committee (IRC); results from the optimisation part are investigator assessed (INV). The CS does not explain why the outcome assessment was different, however, the EAG note that in the study protocol the mantle cell lymphoma cohort of the optimisation part was assessed through IRC. CS Table 13 summarises the analysis sets used for the outcomes in EPCORE NHL-1, the EAG is not able to confirm which analysis sets are presented but assumes from the descriptions these are from the full analyses sets.

The length of follow-up was a median of ■■■ months for the expansion part and 5.7 months for the optimisation part. The median follow-up for the earlier 2023 published data cut was 17.4 months and 5.7 months for the expansion part and optimisation part, respectively.¹⁰

The CS presents results that were adjusted to censor deaths related to the COVID-19 pandemic during the expansion part of the EPCORE NHL-1 study. The CS reports that each mortality event was clinically adjudicated to identify cases where COVID-19 was the cause of death with certainty and censoring for these COVID-19 deaths applied in the survival outcomes (OS, PFS and TTD). The EAG has some reservations about this and asked in clarification A18 for details of how decisions over deaths attributable to Covid-19 were made, and who made the decisions. The company response confirms the decision criteria but does not fully report details of who made the decisions, only that evaluations and adjudications were performed by physicians. The company also states that there are challenges with defining deaths as COVID-19 but that they took a pragmatic approach which was based on the interpretation of their own clinical experts. The EAG clinical experts considered that while it is useful to have the adjusted analyses, there are likely difficulties with confirming that COVID-19 was the cause of death. In addition, the EAG experts considered that there is the possibility that epcoritamab itself increased infection risk and while COVID-19 infections are lower now, there are other infections which can impact mortality. The EAG also notes that in the peer reviewed publication of EPCORE NHL-1 and the CSR from the 2023 data-cut (3L+), the COVID-19 adjusted

analyses were presented as sensitivity analyses, not the main analyses. The EAG was not able to locate details of these COVID-19 adjusted analyses in the statistical analysis plan (version 3.0 dated 8 June 2023) submitted by the company. The EAG view is that the COVID non-modified data is more appropriate but for completeness the EAG also summarises the COVID-modified data as sensitivity analyses.

Table 12: Overview of key efficacy outcomes

	Expansion Part			Optimisation part	
	4L+ n=81 ^a	3L+ n=128 ^{a, b}	3L+ n=128 ^{a, c}	4L+ n=41 ^d	3L+ n=86 ^d
ORR (95% CI) ^e	██████ ████████	██████ ████████	105 (82.0%) (74.3, 88.3)	Not reported	██████ ████████
CR (95% CI) ^e	██████ ████████	██████ ████████	80 (62.5%) 53.5, 70.9)	Not reported	██████ ████████
DOR (months) all responders unmodified analyses					
Median (95% CI) ^f	██████ ████████	██████ ████████	██████ ████████	Not reported	██████ ████████
DOR (months) all responders COVID-19 adjusted analyses					
Median (95% CI) ^f	██████ ████████	██████ ████████	Not reported	NA	NA
DOCR (months) unmodified analyses					
Median (95% CI) ^f	██████ ████████	██████ ████████	██████ ████████	Not reported	██████ ████████
DOCR (months) COVID-19 adjusted analyses					
Median (95% CI) ^f	██████ ████████	██████ ████████	Not reported	NA	NA
PFS (months) unmodified analyses					
Number of events	██████	██████	██████	██████	██████
Number censored	██████	██████	██████	██████	██████
Median (95% CI) ^f	████████ ████████	████████ ████████	████████ ████████	████████ ████████	████████ ████████
PFS (months) COVID-19 adjusted analyses					
Number of events	██████	██████	██████	NA	NA
Number censored	██████	██████	██████	NA	NA
Median (95% CI) ^f	████████ ████████	████████ ████████	████████ ████████	NA	NA

OS (months) unmodified analyses					
Number of events	██████	██████	██████	██████	██████
Number censored	██████	██████	██████	██████	██████
Median (95% CI) ^f	██████████	██████████	██████████	██████████	██████████
OS (months) COVID-19 adjusted analyses					
Number of events	██████	██████	Not reported	NA	NA
Number censored	██████	██████	Not reported	NA	NA
Median (95% CI) ^f	██████████	██████████	Not reported	NA	NA

From CS Table 16; unpublished data supplied in response to clarification A4; CS appendix Table 67; CS appendix Table 69; CS appendix Table 70; CS appendix Table 77; CS appendix Table 81; CSR data cut 2023; Linton 2024;¹⁰ CS Table 40; CS appendix Table 84; CSR optimisation cohort

^aassessed by independent review committee

^bdata cut ████████

^cdata cut 21 April 2023

^dassessed by investigator

^eBased on the Clopper and Pearson method.

^fBased on Kaplan-Meier estimates.

Bold indicates outcomes used in the economic model

CI, confidence interval; CR, complete response rate; DoCR, duration of complete response; DOR, duration of response; FL, follicular lymphoma; NA, not applicable NR, not reached; ORR, overall response rate; PFS, progression free survival.

Response rates

Response rates were largely similar in the 4L+ and 3L+ subgroups of the expansion part (Table 13). An overall response was observed in ██████ of patients in the expansion part 4L+ subgroup. The ORR was not reported in the CS for the latest data cut of the expansion part for the 3L+ subgroup, however, it was 82% in the earlier data cut. The EAG is unable to comment on the 4L+ subgroup of the optimisation part as response rates were not reported. In the 3L+ subgroup of the optimisation part the ORR was ██████████ than reported from the expansion part, at ██████. These ORR rates include participants with a response (complete response (CR) or partial response (PR)) after an assessment of progressive disease or indeterminate response (i.e. pseudoprogression), the EAG has not been able to ascertain any further details of these participants.

In the 4L+ subgroup of the expansion part ██████ achieved a complete response and ██████ a partial response. In the 3L+ subgroup ██████ and ██████ achieved CR and PR

respectively in the expansion part. Rates were [REDACTED] and [REDACTED] in the 3L+ subgroup of the optimisation part.

Table 13: Response rates, unmodified analyses

	Expansion part			Optimisation part	
	4L+ n=81 ^{a,b}	3L+ n=128 ^{a,b}	3L+ n=128 ^{a,c}	4L+ n=41 ^d	3L+ n=86 ^d
ORR^e (95% CI) ^f	[REDACTED]	[REDACTED]	105 (82.0%) (74.3, 88.3)	Not reported	[REDACTED]
CR (95% CI) ^f	[REDACTED]	[REDACTED]	80 (62.5%) 53.5, 70.9)	Not reported	[REDACTED]
PR (95% CI) ^f	[REDACTED]	[REDACTED]	25 (19.5%) [REDACTED]	Not reported	[REDACTED]
Best overall response					
CR	[REDACTED]	Not reported	[REDACTED]	Not reported	[REDACTED]
PR	[REDACTED]	Not reported	[REDACTED]	Not reported	[REDACTED]
SD	[REDACTED]	Not reported	[REDACTED]	Not reported	[REDACTED]
PD	[REDACTED]	Not reported	[REDACTED]	Not reported	[REDACTED]
NE	[REDACTED]	Not reported	[REDACTED]	Not reported	[REDACTED]

From CS Table 16 and 17; unpublished data supplied in response to clarification A4; CSR data cut 2023; Linton 2024;¹⁰ CS appendix Table 84; CSR optimisation cohort

^aassessed by independent review committee

^bdata cut [REDACTED]

^cdata cut 21 April 2023

^dassessed by investigator

^eIncludes participants who had a PR or CR after an assessment of PD or indeterminate response (i.e. Pseudoprogression).

^fBased on the Clopper and Pearson method.

CR: complete response; NE: Not evaluable; OR: overall response; PD: progressive disease; PR: partial response; SD: Stable disease

Time to event results

The following time-to-event outcomes were analysed in EPCORE NHL-1 and presented in the CS document B. The EAG has focused on the 4L+ population for

the in-depth analysis of the survival curves owing to resource and time issues. A summary of the results is presented in Table 14.

Table 14. Summary of time-to-event outcomes in EPCORE NHL-1

Outcome	Follow-up	Median	Responders	Events	Censored
COVID-unmodified					
PFS	██████████ █	██████████ █	█	█	█
OS	██████████ █	██████████	█	█	█
COVID-modified					
DOR	██████████ █	██████████	█	█	█
DOCR	██████████ █	██████████	█	█	█
PFS	██████████ █	██████████	█	█	█
OS	██████████ █	██████████	█	█	█

Duration of response (DOR)

The median DOR for the 4L+ FL cohort, as assessed by IRC using Lugano criteria, was ██████████ at a median follow-up of ██████████. Of the ██████████ responders, ██████ had an event (progression or death), while the remaining were censored.

The Kaplan-Meier plot presented by the company, shown in Figure 1, shows how the curve plateaus at ██████████, suggesting a potentially durable response in a large subset of patients, though longer follow-up is needed to confirm this pattern.

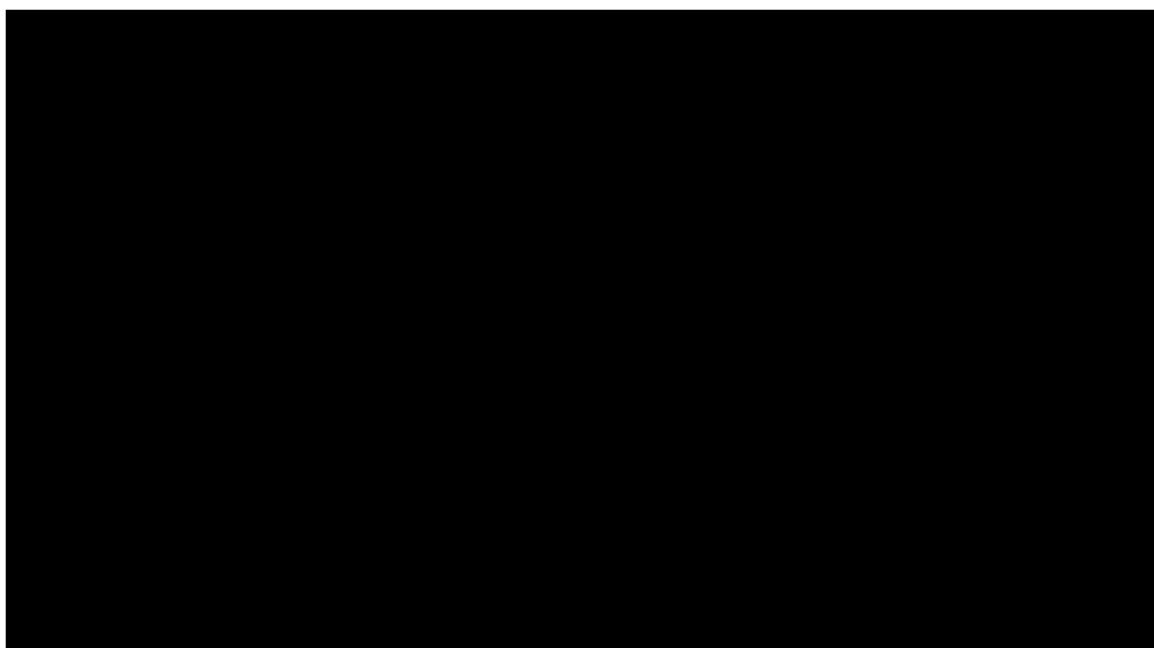


Figure 1. KM of Duration of response (Figure 9 of CS B.2.8.3.1)

Duration of complete responders (DOCR)

The median DOCR for patients with 4L+ FL was NR at a median follow-up of [REDACTED]. Among the [REDACTED] complete responders, [REDACTED] experienced an event while the remaining were censored. The company did not present a Kaplan-Meier plot for this outcome, however the percentages of patients remaining in response was presented in CS Table 18. At 18 months, [REDACTED] of patients remained in complete response. From 24 months onwards this proportion [REDACTED], again suggesting that a large proportion of patients who achieve a complete response may sustain it for a prolonged period.

Progression-free survival (PFS)

Median PFS based on IRC assessment for 4L+ FL was [REDACTED] months, with a median follow-up of [REDACTED] months. Of the 81 patients, [REDACTED] experienced a PFS event (progression or death), while the remaining were censored. Censoring was primarily due to data cut-off [REDACTED], followed by initiation of new anti-lymphoma therapy (13.6%) or other reasons ([REDACTED]). KM estimates showed that [REDACTED]% of patients remained progression-free at 6 months, eventually plateauing at [REDACTED]% from 30 months onwards.

The company presented the COVID-modified curves in response to CQ A23, with the accompanying KM plot as shown below in Figure 2. Both curves begin to

separate at about nine months, with a consistent separation forming from around 12-15 months onwards. [REDACTED] was recorded as having progressed at the time of a COVID-related death, and [REDACTED] of the [REDACTED] COVID-19 deaths occurred in patients who were in CR, which, according to the company suggests that these patients would likely have had extended PFS if not for COVID-19. This trend aligns with the company's clinical expert opinion that patients achieving CR generally have a low risk of progression.

Overall, the data suggest that epcoritamab produces durable disease control in a substantial proportion of patients, with nearly half remaining progression-free at 3 years, though COVID-19 mortality has introduced some confounding in longer-term estimates.

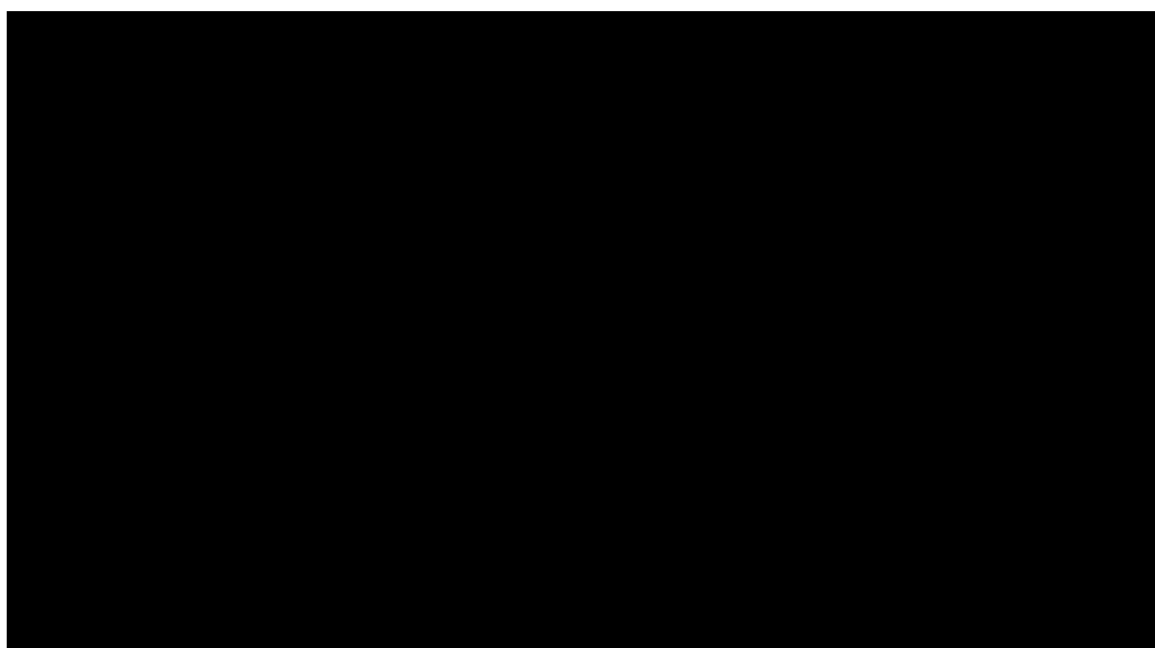


Figure 2. KM of Progression-free survival including COVID-modified adjustment (Figure 2 of CS Clarification Responses)

Overall survival (OS)

As of the [REDACTED] data-cut, [REDACTED] of the 81 4L+ FL patients had died, with a median follow-up of [REDACTED]. Median OS was [REDACTED], indicating that [REDACTED]. The estimates from the KM plot show high survival in early follow-up, with [REDACTED]% of patients alive at 18 months and [REDACTED]% alive at 36 months.

The company adjusted the OS results to account for COVID-19 deaths as outcomes in EPCORE NHL-1 were recorded during the COVID-19 pandemic. A total of █ deaths were clinically adjudicated, by the company's experts, as attributable to COVID-19, of which █ occurred during the Omicron wave, and █ of these █ patients were in CR at the time of death. The company argued that since patients in CR typically exhibit significantly better long-term survival, the inclusion of these deaths skews the OS curve downward, underestimating treatment benefit.

Therefore, the company censored these patients at the times of their death, instead of treating them as a death, in this new COVID-modified dataset. A comparison of the KM plots for both datasets, original and COVID-modified, is presented in Figure 3. As with PFS, a visible separation emerges in the KM curves between the unmodified and modified OS estimates between 12 to 15 months, suggesting that COVID-19 had an impact on survival outcomes. The company report that █ deaths were attributable to COVID-19, representing █% of the starting population. The company states that █ of these people were in complete response when they died. This approach was aligned with the method used in Linton et al. 2024, which conducted COVID-19 sensitivity analyses using stringent adjudication criteria for censoring. The Linton appendix outlines how deaths were identified for censoring, including:

- Deaths in patients with probable or confirmed COVID-19,
- Deaths linked to relevant medical system organ classes (e.g. respiratory or cardiac) in COVID-positive patients, or
- Any death with COVID-19 mentioned in free-text cause.

In those cases, if no alternative non-COVID cause of death was clearly present, the death was censored at the date of death for all time-to-even outcomes.

The EAG is unsure of the frequency of monitoring, and how recent the CR was confirmed. Without knowing how up to date their response status was, there remains some uncertainty about the accuracy of assuming these patients would have remained long-term responders.

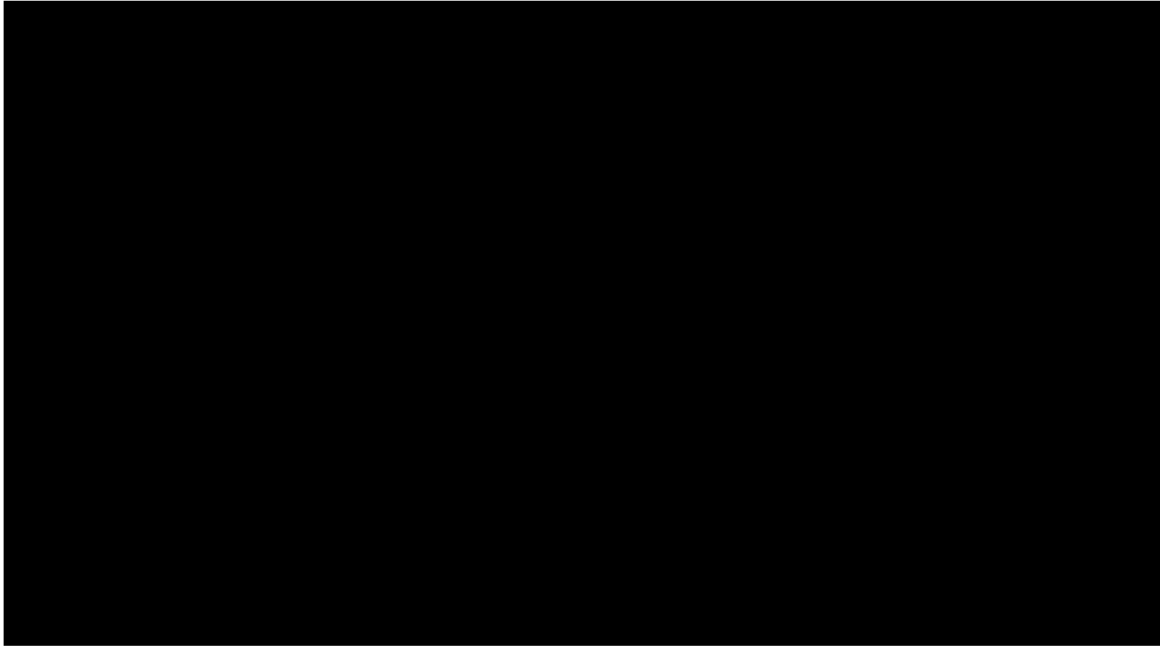


Figure 3. KM of Overall survival including COVID-modified adjustment (Figure 7 of CS B.2.6.1)

HRQoL results

HRQoL is reported for the Expansion 4L+ subgroup in CS section 2.8.4. HRQoL outcomes are not presented in the CS for the Expansion 3L+ subgroup, but are available in the CSR provided by the company for the earlier data-cut of 21 April 2023. HRQoL does not appear to have been measured in the Optimisation part of EPCORE NHL-1 and the EAG is not aware of any peer review full publications of HRQoL outcomes from EPCORE NHL-1.

For the 4L+ subgroup, the CS states that HRQoL measured by the Functional Assessment of Cancer Therapy-Lymphoma subscale (FACT-LymS) was maintained throughout the study (CS Figure 12). Also, that EQ-5D utility scores (an exploratory outcome) improved from [REDACTED] (SD: [REDACTED]) at baseline to [REDACTED] (SD: [REDACTED]) at the end of treatment. However, the EAG notes that this

[REDACTED]
[REDACTED]
[REDACTED] The number of patients in the analysis set for EQ-5D was [REDACTED] at baseline, [REDACTED] at Cycle 3, and [REDACTED] at Cycle 9, so only half of patients had an assessment by Cycle 9.

FACT-Lym also consists of a 27-item general quality of life instrument (FACT-G) and this was used in the study,³¹ however results were not reported in the CS. Data were provided by the company in tabular form at Clarification (A4). Mean change from baseline to end of treatment was [REDACTED]. The MID was not reported. FACT-Lym Trial Outcome Index (TOI) and FACT Lym Total score were also reported in the tables provided at Clarification and showed little change from baseline at end of treatment.

For the 3L+ subgroup, at the 2023 data cut, the completion rate for FACT-Lym ranged from [REDACTED] at baseline to [REDACTED] at Cycle 9. Compliance rate was [REDACTED] at most time points.

[REDACTED]
[REDACTED]
Completion rates for EQ-5D-3L among the 3L+ subgroup ranged from [REDACTED] at baseline to [REDACTED] at Cycle 9. Mean EQ-5D utility scores improved from [REDACTED] (SD

████) at baseline to █████ (SD █████) at Cycle 1. The change was less than the MID (████).

The use of EQ-5D-3L data in the company's economic model is discussed in section 4.2.7.

3.2.6 Subsequent therapies

Table 15 shows various subsequent therapies received in the 4L+ and 3L+ expansion parts. Although other specific therapies were reported, the EAG focused on those included in Table 15, as they were used in the economic modelling (Further discussed in EAG report section 4.2.8). The EAG was able to validate data for the 4L+ subgroup with that of the abbreviated dataset provided at clarification question A4. For the 3L+ subgroup, data from the 2024 cut could not be verified due to the lack of a CSR or publication. However, the 2023 data for the 3L+ subgroup were available in the 2023 CSR but not in the publication by Linton et al.¹⁰

A slightly higher proportion of patients in the 3L+ subgroup of the expansion part (approximately █████ received subsequent therapies in both the 2024 and 2023 data cuts, compared with (████) in the 4L+ subgroup. In the 4L+ subgroup, there is a higher proportion of events (████) with 'new anti-lymphoma' therapies used for the outcome Time to Next Lymphoma Therapy (TTNT) (CS Table 23) than the proportion of subsequent therapies received (████, Table 15). This discrepancy may suggest that some patients received more than one treatment; however, the numbers do not align exactly.

Systemic drugs were commonly used across both subgroups, with the highest proportion observed in the 4L+ subgroup (████). In both subgroups rituximab was the most commonly used subsequent systemic therapy; in the 4L+ subgroup rituximab was used by █████ of patients, and █████ in the 3L+ subgroup. A greater proportion of patients in the 4L+ subgroup received CAR-T therapy (████) than allogeneic stem cell transplant (allo-SCT) (████). In the 3L+ subgroup, CAR-T therapy and allo-SCT were received by █████ and █████, respectively, with no change between the data cuts. The use of other therapies was broadly similar across the subgroups.

Table 15: Subsequent therapies in expansion part: 4L+ and 3L+ subgroups

	<i>Expansion part, 4L+ (N = 81)^{a,b}</i>	<i>Expansion part 3L+ (N = 128)^c</i>	<i>Expansion part 3L+ (N = 128)^d</i>
Starting subsequent treatment n (%)			
Allogeneic stem cell transplant (allo-SCT)			
Systemic drugs (any)			
Rituximab			
Cyclophosphamide			
Doxorubicin			
Vincristine			
Bendamustine			
Lenalidomide			
CAR-T therapy			

^a The number of events reported in CS document B, section 2.9, Table 22 for 4L+ is higher than in CS document B, section 2.9.1 Table 23. This discrepancy may reflect multiple subsequent treatments per patient; however, the figures do not align directly. The EAG requested clarification on this point (clarification question A19, 20)

^b The EAG verified this data with the abbreviated dataset provided at clarification question A4 and notes that this dataset was not the CSR.

^c The EAG was unable to verify data for the 3L+ subgroup derived from the [REDACTED] data cut, as the available CSR was based on the 2023 data cut.

^d Data was derived from the 2023 data cut and verified using the available CSR, 2023. However, the EAG could not verify this data with the publication,¹⁰ as it was not reported.

3.2.7 Adverse events

A CSR for the Expansion 4L+ subgroup was not provided with the original CS, however the company stated they do not have a CSR for this subpopulation and an abbreviated report of relevant tables was provided in response to Clarification A4. The EAG has checked data where available.

For the Expansion 3L+ subgroup, the data cut reported in the CS is [REDACTED], whereas the CSR data cut is 21 April 2023. The EAG is therefore unable to validate the adverse event data in the CS. Median follow-up for the Expansion part was [REDACTED].

The CS and CSR have the same data cut for the Optimisation 3L+ subgroup, and data have been checked. Median duration of follow-up was 5.7 months. CS p111 states 'Safety outcomes for the 4L+ Optimisation subgroup are unavailable at the time of submission'.

For completeness, the EAG requested adverse event data for the 3L-only subgroup of the Expansion and Optimisation parts (Clarifications A5 and A8), however the company did not provide these.

Summary

An overview of adverse events for each of the subgroups is presented in Table 16; these are discussed in further detail below. Events tended to be [REDACTED] in the Optimisation 3L+ subgroup; the reasons for this are unclear. It may be related to the [REDACTED] follow-up and slower dosage escalation,

Table 16: Overview of TEAEs

	Expansion Part ^a		Optimisation Part ^b
	4L+ (N = 81)	3L+ (N = 128)	3L+ (N = 86)
Number of Patients with at least one, N (%)			
TEAE	[REDACTED]	[REDACTED]	[REDACTED]
Related TEAE	[REDACTED]	[REDACTED]	[REDACTED]
Grade 3 and higher TEAE	[REDACTED]	[REDACTED]	[REDACTED]
Grade 3 and higher related TEAE	[REDACTED]	[REDACTED]	[REDACTED]
TEAE by worst toxicity grade, N (%)			
1	[REDACTED]	[REDACTED]	[REDACTED]
2	[REDACTED]	[REDACTED]	[REDACTED]
3	[REDACTED]	[REDACTED]	[REDACTED]
4	[REDACTED]	[REDACTED]	[REDACTED]
5	[REDACTED]	[REDACTED]	1
Serious TEAE	[REDACTED]	[REDACTED]	[REDACTED]
Serious TEAE-related to epcoritamab	[REDACTED]	[REDACTED]	[REDACTED]
TEAE leading to treatment discontinuation	[REDACTED]	[REDACTED]	[REDACTED]
TEAE leading to dose delay	[REDACTED]	[REDACTED]	[REDACTED]
Fatal TEAE	[REDACTED]	[REDACTED]	1
Fatal TEAE-related to epcoritamab	[REDACTED]	[REDACTED]	1
AESIs, N (%)			

Further information on Grade 3 or 4 TEAEs that were used in the company's economic model (see section 4.2.7.4) for the 4L+ subgroup is presented in CS Table 58 and is summarised in Table 17 below, together with data for the other subgroups. These data were not presented in the report provided by the company in response to Clarification A4, so the EAG was unable to validate the data. Proportions of adverse events were mostly similar between the 4L+ and 3L+ subgroups of the Expansion part. The most common Grade 3-4 TEAE was [REDACTED] (Expansion 4L+: [REDACTED] 3L+: [REDACTED]; Optimisation 3L+ [REDACTED]).

Treatment-related Grade 3-4 TEAEs are also presented in the CS for the Expansion part (CS Table 34, CS Appendix Table 74), and are available in the CSR for C1-Opt 3L+ but have not been reproduced here.

The EAG also requested Grade 3+ AEs used in the model for the LBCL and MCL populations of EPCORE NHL-1 for completeness (Clarification A9), but the company did not provide these.

The EAG considered Grade ≥ 3 TEAEs occurring in the whole LBCL cohort (N=157) at the January 2022 data-cut³² and at two- year follow-up¹⁷ for comparison. The EAG notes that anaemia was slightly more common than the value used in the company's economic model (10.2% [2022 ref] and 12.1% [2024 ref] vs [REDACTED]). In addition, thrombocytopenia occurred at a rate of 5.7% [2022 ref] and 5.1% [2024 ref], but this was not included in the company's economic model.

Table 17: Grade 3 or 4 TEAEs

	Expansion Part ^a		Optimisation Part ^b
Grade 3 or 4 TEAEs ^c	4L+ (N=81) ^c	3L+ (N = 128) ^c	3L+ (N = 86) ^c
≥ 1 grade 3 or 4 TEAE	[REDACTED]	[REDACTED]	[REDACTED]
Anaemia	[REDACTED]	[REDACTED]	[REDACTED]
COVID-19	[REDACTED]	[REDACTED]	[REDACTED]
COVID-19 pneumonia	[REDACTED]	[REDACTED]	
Leukopenia/Leukocytopenia	[REDACTED]		

Lymphopenia	■	■	■
Lymphocyte count decreased		■	■
Neutropenia	■	■	■
Neutrophil count decreased	■	■	■
Pneumonia	■		
Thrombocytopenia			■
Hyperglycaemia			■
Hypokalaemia			■

Source: CS Table 32, CS Table 58, CS Appendix Table 74, CSR Table 12-5. ^a Data cut ■.

^b Data cut 8 January 2024. ^c Occurring in ≥5% of Expansion 4L+ and 3L+; ≥2% of C1-OPT 3L+.

TEAEs, treatment-emergent adverse events.

TEAEs leading to discontinuation

TEAEs leading to discontinuation are presented in the CS for the Expansion subgroups only, in CS Table 35 (Expansion 4L+) and CS Appendix Table 75 (Expansion 3L+). Data for Optimisation 3L+ is available in the CSR (CSR 12.1.7). The most common event leading to trial discontinuation in the Expansion part was COVID-19 pneumonia (■) or COVID-19 (■). Other TEAEs leading to discontinuation occurred in ■ participants. In the Optimisation part 3L+, ■ of participants had a TEAE that lead to discontinuation (■).

AESI

Adverse events of special interest included Immune Cell Associated Neurotoxicity Syndrome (ICANS) and CRS. These are reported in CS Table 36 (Expansion 4L+), CS Appendix M Table 76 (Expansion 3L+) and CS Appendix M Table 92 (Optimisation 3L+). At least one ICANS event occurred in ■ of Expansion 4L+, 3L+ and Optimisation, respectively. ■. At least one CRS event occurred in ■ of each subgroup, respectively.

■.

3.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

EPCORE NHL-1 is a single-arm study and the company's SLR did not identify any studies that were suitable comparators in the 4L+ population (see section 3.1 [Critique of methods of review]). As outlined in the company's decision problem (section 2.3), the most appropriate comparator was considered to be a basket of care. The company therefore engaged with the Haematological Malignancy Research Network (HMRN) to establish a dataset for use as a comparator in the MAIC. A confidential report was provided by the company.⁴

HMRN

The HMRN region covers Yorkshire and the Humber & Yorkshire Coast Cancer Networks in the UK, with a total population of 3.8 million. The HMRN provides information and statistics primarily based on a population-based cohort which comprises all patients diagnosed with a haematological malignancy or related precursor condition; patients enter the cohort on the day they are diagnosed and are regularly followed up. The cohort has a similar age and sex profile to the UK, and a comparable socioeconomic and urban/rural distribution, which the HMRN says means that the findings can be generalised to the whole country.⁴ The HMRN receives funding from non-commercial sources.

The analysis conducted for the company identified people newly diagnosed with FL between 1st September 2004 and 31st December 2021, aged ≥18 years at diagnosis, and who had received ≥3 lines of chemotherapy.

The EAG has cross-checked data cited in the CS (PFS, OS, baselines in CS Table 28) against the HMRN report.⁴

Baseline characteristics are discussed further in section 3.4.2.

The EAG notes that some of the interventions received at 4L+ are not in line with the NICE scope for this appraisal, however this is not unexpected given the inclusion

period (2004 to 2021) and the lack of SOC at this line. These are summarised in section 3.4.2.

Key results from the HMRN report for 4L+ FL patients are presented in Table 18 and Table 19. Of the █ patients in the 4L+ setting, █ patients achieved a complete response, █ achieved a partial response, █ patient had stable disease, and █ patients progressed disease. █ patient's response to treatment was not evaluable, though the reason was not given, and █ patient did not discontinue and was still ongoing treatment.

The results from the HMRN indicate the █ did not respond well to treatment, potentially underscoring the unmet need in the 4L+ setting. █ of the patients experienced progressive disease, suggesting limited effectiveness of the current batch of available treatments in this real-world cohort. Furthermore, █ had discontinued treatment, suggesting that the current available treatments were either not tolerable, not effective, or both.

Table 18. Response to treatment from the HMRN report

	N = █	Treatment discontinued	
		No	Yes
Complete response	█	█	█
Partial response	█	█	█
Stable disease	█	█	█
Progressed disease	█	█	█
Not evaluable	█	█	█
Ongoing treatment	█	█	█

In this cohort, median PFS was █ months with █ patients progressing at the time of analysis, median OS was █ months with █ deaths, and median TTD was █ months with █ patient discontinuing treatment.

Results of the time-to-event outcomes, [REDACTED], reinforce the poor prognosis and limited treatment durability for patients with 4L+ FL in real-world clinical practice.

Table 19. Results of time-to-event outcomes from the HMRN report

	Median	Responders	Events	Censored
PFS	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
OS	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
TTD	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

3.4 Critique of the indirect comparison and/or multiple treatment comparison

No meta-analysis was performed by the company due to EPCORE NHL-1 being a single-arm study, and no head-to-head trials were identified by the company's search strategy. Therefore, the company performed a matching adjusted indirect comparison (MAIC) using individualised patient data (IPD) from EPCORE NHL-1 to match the population of the COVID-modified dose-expansion cohort of EPCORE NHL-1 to current 4L+ care in England.

MAICs involve reweighting IPD from one study to match the baseline characteristics of a comparator study, enabling a fairer comparison between treatments. In this STA, IPD were used from EPCORE NHL-1 to reweight the COVID-modified dose-expansion cohort to match important treatment effect modifiers (TEMs) from the HMRN. The quality of the comparison after adjusting for TEMs depends on the overlap between populations, indicated by the choice of variables used for matching and how the effective sample size (ESS) post-matching changes from the original sample size of the study in question, in this case EPCORE NHL-1. An unanchored MAIC, such as this, also requires all prognostic factors to be included in the analysis.

The company considered implementing a simulated treatment comparison (STC). STCs, like MAICs, are also used when head-to-head clinical trial data are unavailable. The company's reasons for not doing a STC include the small number of events in EPCORE NHL-1 which limits the feasibility of an STC, which relies on

the number of events to determine how many predictors can be included; MAICs are thought to be better for assessment of effectiveness against a single comparator or single real world evidence (RWE) result (as in HMRN) whereas STCs are better suited for multiple comparators; STCs require selecting a parametric distribution adding further complexity; and MAICs have frequently been accepted in prior STAs of FL treatments.

The EAG presents a summary of the trials included in the MAIC. The safety and efficacy of epcoritamab was from the COVID-modified dose-expansion cohort of EPCORE NHL-1, and the safety and efficacy of the current 4L+ care in England was from a report by the Haematological Malignancy Research Network (HMRN).

3.4.1 Comparison of included studies

There are several important differences between the EPCORE NHL-1 trial and the HMRN dataset that raise concerns regarding the validity of the company's MAIC, see

Table 20. EPCORE NHL-1 is a multinational, phase 2, open-label clinical trial where data is collected prospectively, compared to HMRN which is a retrospective, observational dataset limited to two regions in England. The studies differ in sample size and median follow-up, and the difference in study period might generate differences in outcome simply due to changes in clinical practice and standards of care.

The patient populations may also differ due to the inclusion criteria. EPCORE NHL-1 included a more selectively defined group (4+ prior therapies and relapsing remitting (R/R) disease), whereas the HMRN included patients with 3+ lines of therapy, potentially capturing a broader and more heterogeneous group – though the MAIC included the 4L+ patients in HMRN. Treatments received in the HMRN report were also more varied with no defined standard comparator, compared to EPCORE NHL-1 which used epcoritamab as the only treatment option.

Table 20: Study design of EPCORE NHL-1 and the HMRN report

Study design	EPCORE NHL-1	HMRN
Population	COVID-modified post-expansion phase 4L+ FL	4L+ FL

Study design	EPCORE NHL-1	HMRN
		engaged with HMRN for the data for the ITC.
^A The HMRN uses ICD O-3 codes of 9579, 9690, 9695, and 9698. There was no code for 9579, suggesting that some were not FL grade 1-3a. The EAG notes that code 9579 does not exist in ICD O-3; it is unclear if this is a typographical error or other error. Abbreviations: R-CVP: Rituximab + cyclophosphamide, vincristine and prednisolone; R-CHOP: Rituximab + cyclophosphamide, doxorubicin, vincristine and prednisolone; R-Benda: Rituximab + bendamustine; FCR: fludarabine, cyclophosphamide, rituximab; RTX: radiotherapy; R-DHAP: Rituximab + dexamethasone, high-dose cytarabine, and cisplatin; R-GDP: Rituximab + gemcitabine, dexamethasone, cisplatin; R2: Rituximab + lenalidomide		

3.4.2 Comparison of Baseline Characteristics

Table 21 compares the baseline characteristics between EPCORE NHL-1 and the HMRN and notes the important treatment effect modifiers (TEMs) as identified by the company in CS B.2.12.2.2. One issue was the lack of reporting for the HMRN. Variables such as race, ethnicity, BMI, renal and hepatic function were not reported in the HMRN.

While median age and sex distribution appear [REDACTED]. A comparison of available prognostic indicators showed that ECOG and FLIPI score, at diagnosis in the HMRN cohort were slightly better than the 4L+ EPCORE NHL-1 population. However, EAG clinical experts stated these scores were likely to worsen as patients moved through lines of therapy, and so this comparison could be misleading.

POD24 (disease progression within 24 months of front-line chemoimmunotherapy)³³ was [REDACTED] in the HMRN dataset while EPCORE NHL-1 included [REDACTED] double-refractory patients (patients who did not respond to both anti-CD20 and an alkylator). [REDACTED] patients in EPCORE NHL-1 received four or more prior lines of therapy, and there were more [REDACTED]. Furthermore, stem cell transplant was [REDACTED] in the HMRN cohort.

Table 21: Comparison of baseline characteristics of EPCORE NHL-1 and the HMRN report

	EPCORE NHL-1 Expansion Part	HMRN	Treatment effect modifier	
	4L+ FL (N = 81)	4L+ ████	Identified as TEM by company's experts	Included in MAIC
Age at informed consent (years)			Y	Y
Mean (SD)	64.8 (11.06)	NA		
Median	66.0	████		
Min, Max	39, 84	IQR █████		
Sex (at birth)			Y	Y
Male	53 (65.4%)	████		
Female	28 (34.6%)	████		
Race			N	N
White	51 (63.0%)	NR		
Black or African American	0	NR		
Asian	3 (3.7%)	NR		
Other	0	NR		
Not reported	27 (33.3%)	NR		
Ethnicity			N	N
Hispanic or Latino	0	NR		
Not Hispanic or Latino	12 (14.8%)	NR		
Not reported	1 (1.2%)	NR		
BMI (kg/m²) category at baseline			N	N
<18.5	1 (1.2%)	NR		
18.5 ≤ 25.0	39 (48.1%)	NR		
25 ≤ 30	27 (33.3%)	NR		
≥ 30.0	14 (17.3%)	NR		
ECOG Performance status		At diagnosis	Y	N
0	40 (49.4%)	████		
1	38 (46.9%)	████		
2	3 (3.7%)	████		
3/4	NA	████		

	EPCORE NHL-1 Expansion Part	HMRN	Treatment effect modifier	
	4L+ FL (N = 81)	4L+ ████	Identified as TEM by company's experts	Included in MAIC
Unknown	NA	████		
Baseline renal function classification by Cockcroft- Gault method (CrCl)[mL/min]			N	N
Normal (≥ 90)	27 (33.3%)	NR		
Mildly impaired (60≤ 90)	38 (46.9%)	NR		
Moderately impaired (30 ≤ 60)	16 (19.8%)	NR		
Severe impairment	0	NR		
Baseline hepatic function per NCI criteria			N	N
Normal	65 (80.2%)	NR		
Mild Dysfunction	16 (19.8%)	NR		
Moderate dysfunction	0	NR		
Severe dysfunction	0	NR		
Disease type at trial entry			Y	Y
FL Grade 1-3A	81 (100%)	NR ^A	N	N
Histological grade				
1	9 (11.1%)	NR		
2	45 (55.6%)	NR		
3A	27 (33.3%)	NR		
Not applicable	0			
Median time for initial dose to first dose ^a (years)	0			
FLIPI		At diagnosis	Y	N
0-1	11 (13.6%)	Low: █████		
2	13 (16.0%)	Intermediate: ████		
≥3	57 (70.4%)	High: █████		
Unknown	0	████		
Not applicable	0	NR		

	EPCORE NHL-1 Expansion Part	HMRN	Treatment effect modifier	
	4L+ FL (N = 81)	4L+ ██████	Identified as TEM by company's experts	Included in MAIC
POD24			Y	Y
Progression, transformation or relapse within 24 months of initiating first-line immunochemotherapy	30 (37.0%)	POD24 (CIT first line): ████████		
Double refractory disease				
Double refractory to anti-CD20 and alkylating agents, regardless of two treatments being in the same or different treatment lines	60 (74.1%)	Double refractory: ██████ Double refractory ≥2 prior lines ██████	Y	Y
Bone Marrow Involvement		At diagnosis	N	N
Bone marrow involvement at baseline by investigator	26 (32.1)	██████████		
Prior therapy				
Stem cell transplant	██████	██████	Y	Y
CAR-T	██████	█	Y	Y
Radiotherapy	Awaiting CSR	NR	N	N
Prior lines of therapy	41 (50.6)	██████████	Y	Y
3	40 (49.4%)			
≥4				
^ Eligibility stated FL diagnosis recorded by WHO ICD-O-3 codes of 9579/3; 9690/3; 9695/3; 9698/3. These correspond to diagnosis of not listed, FL NOS, FL grade 1 and FL grade 3 respectively				

3.4.3 Variables included in MAIC

The company discusses the choice of variables in CS B.2.12.2.2 and originally considered: age, sex, ECOG performance status, disease stage, FLIPI score, rapid progression on prior treatments, number of prior treatments, previous treatment with specific therapies, and refractory status. These factors aligned with the TEMs considered in the MAIC conducted in TA627.

The reliability of the MAIC was limited by the lack of reporting in the HMRN dataset, where some variables were not reported or others like ECOG status or FLIPI, were measured at baseline but not at the start of 4L+ therapy. The company noted that age and disease stage are components of the FLIPI score and therefore were indirectly adjusted for through inclusion of FLIPI in the analysis. As such, the company did not consider their omission to substantially bias the analyses. The EAG clinical experts stated that the reliability of an indirect comparison would be further negatively impacted by missing these important prognostic factors, in addition to the differences in inclusion/exclusion criteria applied to the two populations.

The final analysis was conducted using the following TEMs: age (≥ 60 years), disease stage 3-4, sex, prior autologous stem cell transplantation (ASCT), prior chimeric antigen receptor T-cell therapy (CAR-T), prior lines of therapy ≥ 4 , progression of disease within 24 months (POD24) after first line chemotherapy induced therapy (CIT), refractory to both anti-CD20 and alkylator therapy, refractory to most recent anti lymphoma therapy, and prior treatment with combination of rituximab and lenalidomide (R²). Table 27 of the CS presents the selection of the TEMs with reasons for inclusion or exclusion.

Prior to matching, there were notable differences between the epcoritamab trial population and the HMRN comparator cohort across several key baseline characteristics. The percentage of patients in HMRN with advanced-stage disease (stage 3-4) was [REDACTED] than in EPCORE NHL-1 ([REDACTED] vs [REDACTED], respectively). Prior CAR-T therapy was reported in [REDACTED] of EPCORE NHL-1 patients, but was [REDACTED] in HMRN, suggesting a [REDACTED] in access for advanced treatments. Prior treatment with R2 (lenalidomide and rituximab), was [REDACTED] in EPCORE NHL-1 than in HMRN with limited 95% CI overlap, as with patients with 4+ prior lines of therapy. These differences raise concerns about residual imbalances in disease

severity and prior treatment exposure, which may affect the validity of the estimates derived from the MAIC.

There were no statistically significant differences between the other TEMs, which included the proportions of people aged 60 years and over, males, prior CAR-T, POD24 after 1L chemoimmunotherapy (CIT), and refractory to both anti-CD20 and an alkylator.

Table 22. Comparison of TEMs at baseline pre-MAIC-adjustment*

	Epcoritamab FL (n = 81)	HMRN (n = 10)
Age ≥ 60	69.1% (58.4% to 78.2%)	██████████
Male	65.4% (54.5% to 75.0%)	██████████
Disease Stage III – IV	85.2% (75.7% to 91.6%)	██████████
Prior ASCT	18.5% (11.5% to 28.3%)	██████████
Prior CAR-T	7.4% (3.2% to 15.7%)	██████████
POD24 after first line CIT	37.0% (26.9% to 48.3%)	██████████
Refractory to most recent anti-lymphoma therapy	76.5% (66.2% to 84.7%)	██████████
Refractory to both anti-CD20 and an alkylator	74.1% (63.5% to 82.7%)	██████████
Prior lines of therapy ≥4	49.4% (38.4% to 60.5%)	██████████
Prior treatment with R2	30.9% (21.7% to 41.9%)	██████████
95% confidence intervals estimated using normal approximation to the binomial distribution, using $CI = p \pm 1.96 \times \sqrt{\frac{p(1-p)}{N}}$		

3.4.4 Post-MAIC outcomes

The EAG show the estimates of relative efficacy coming from the MAIC analysis in Table 23, including the estimates from the company clarification response A25 which did not censor COVID-related deaths, and the results where the COVID-related deaths during the Omicron wave of the COVID-19 pandemic were censored. The application of MAIC weights led to HRs that indicated ██████████ of epcoritamab than in the unadjusted analysis. While this is not inherently implausible, it was an unexpected result given the differences between the trial and real-world comparator populations. This direction of effect also ██████████ with the findings of

most MAICs in the HTA process and in the literature, where adjustment typically results in [REDACTED], not [REDACTED].. The effective sample size (ESS) for the company's preferred MAIC was 40.

Table 23: Outcomes from MAIC analysis

Outcome	EPCOR E NHL 1 (pre-MAIC)	EPCORE NHL 1, including COVID deaths (pre-MAIC)	Omicron - modified (pre-MAIC)	EPCOR E NHL 1 (post-MAIC)	EPCORE NHL 1, including COVID deaths (post-MAIC)	Omicron - modified (post-MAIC)	HMRN
PFS hazard ratio vs HMRN (95% CI)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
OS hazard ratio vs HMRN (95% CI)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Overall response [odds ratio (95% CI)]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Complete response [odds ratio (95% CI)]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

In response to clarification question A24, the company demonstrated stability of the estimates when the variables included in the MAIC were varied, however these analyses were limited in the scenarios that were explored. The first included matching the proportions of patients with ECOG (=0) and FLIPI (=3-5) scores using the scores at diagnosis for the HMRN population (ESS=28. The second used alternative variables to measure refractory status (ESS=31).

From these results, the company concludes that epcoritamab is superior and carries the output from the MAIC analyses into the cost-effectiveness modelling.

3.4.5 EAG Critique of MAIC

The EAG has a number of concerns about the MAIC which question its suitability for decision-making. Firstly, the small effective sample size for the MAIC weighted population, plus the small sample size of HMRN cohort means the true estimate of relative efficacy is unlikely to be represented and could be influenced by the outcomes of a small number of individuals. Secondly, the methodology of the MAIC is unlikely to account for the differences between a trial and real-world population, particularly the stricter inclusion/exclusion criteria of the EPCORE NHL-1 trial. Known key prognostic factors are unable to be included in the MAIC. While the MAIC may be a theoretically appropriate method in the absence of direct comparative data, its implementation in this submission is fundamentally limited by data constraints and uncertain assumptions.

Finally, the EAG considers it implausible that the application of weights to a trial dataset, when matching to real-world evidence, would improve the efficacy of epcoritamab. The EAG interprets this as evidence that the MAIC results lack face validity.

For these reasons, the EAG considers the MAIC to be unhelpful and potentially misleading for decision-making purposes. Whilst a naïve comparison clearly has its limitations, the EAG considers this the strongest evidence to inform relative efficacy. The company could explore applying a simulated treatment comparison³⁴ however this would be limited to the same covariates as the MAIC, so is not an obvious improvement over a naïve comparison.

The company's preference to use of the COVID-modified cohort is also a concern. The EAG understands that the HMRN cohort was also likely impacted by COVID, and so to remove these events in one source may introduce bias to the analysis by increasing the likelihood of more negative outcomes in the HMRN group. Additionally, COVID deaths were adjudicated using prespecified and physician-led criteria; however, censoring all deaths in this category may still risk introducing bias,

particularly as COVID-related deaths were not similarly censored in the HMRN comparator cohort.. The EAG prefers to use the non-COVID adjusted analysis in a naïve comparison.

3.5 *Additional work on clinical effectiveness undertaken by the EAG*

The EAG updated the company's MEDLINE and Embase searches, to check for any new publications. Two additional studies were identified as potentially relevant (Day 2025³⁵ and Gao 2025³⁶), but were excluded after examination of the full paper. Two recent abstracts were also identified (via Google Alerts) that may be useful if the 3L+ population is to be considered.^{23, 24}

The EAG also conducted targeted searches to check for any relevant studies missed due to identified limitations in the company's search strategies. Only one publication of relevance was identified, a RWE study of quality of life in patients with FL in Europe (including the UK) and USA (Johnson 2024).²² The EAG considers that this study could be useful should there be a focus on the 3L+ population, although notes that HRQoL was not assessed in response to a treatment and that various treatments had been given at 1L and 2L so may not reflect the current treatment pathway. Search strategies for additional searches run by the EAG can be found in Appendix 8.1.1

3.6 *Conclusions of the clinical effectiveness section*

The CS presents direct evidence from the EPCORE NHL-1, an ongoing open label multinational single arm phase 2 study evaluating the safety and efficacy of epcoritamab in R/R patients with B-cell lymphomas, including FL grades 1 – 3A among adults having exhausted all previous lines of therapy (subgroup of relevance to the decision problem in this submission). The study was divided into three parts of which the expansion and optimisation parts within the 4L+ and 3L+ subgroups of patients with FL relevant to this submission. While the CS focussed on outcomes for the 4L+ subgroups, the EAG also considered those of the 3L+ subgroup.

Primary efficacy outcomes across subgroups are reported as follows: In the expansion 4L+ subgroup (latest data cut), an overall response rate (ORR) of [REDACTED] was observed. ORR for the 3L+ subgroup was not

reported in the latest data cut, but an ORR of 82% was noted in an earlier analysis. No ORR data were reported for the 4L+ optimisation cohorts, while the ORR for the 3L+ optimisation cohort was [REDACTED], at [REDACTED] compared with the expansion part. A complete response [REDACTED] and [REDACTED] partial response was also observed in the expansion cohort 4L+ subgroup, while in the 3L+ subgroup: [REDACTED] and [REDACTED] achieved CR and PR, respectively. Rates for CR and PR in the 3L+ optimisation phase were [REDACTED] and [REDACTED], respectively. The EAG consider the non-adjusted COVID-19 data for the survival analysis to be the more appropriate source of evidence, as it better reflects real-world trial conditions and avoids introducing bias by selectively censoring deaths, given the uncertainty around the timing and confirmation of CR in those who have died of COVID-19.

The most frequent adverse events for each subgroup were CRS (expansion 4L+ [REDACTED] 3L+ [REDACTED] optimisation [REDACTED]), fatigue (expansion 4L+ [REDACTED] 3L+ [REDACTED] optimisation 3L+ [REDACTED]), COVID-19 (expansion 4L+ [REDACTED] 3L+ [REDACTED] optimisation 3L+ [REDACTED]), and injection site reactions (expansion 4L+ [REDACTED] optimisation [REDACTED]).

Overall, the EAG has no major concerns about the EPCORE NHL-1 risk of bias. However, the EAG notes that patient characteristics of those lost to follow-up were not described, neither were characteristics of censored patients, thus limiting the ability to fully assess the impact of incomplete follow-up. Although there was a difference between the dose escalation used in the expansion phase (efficacy data) and the [REDACTED] optimised regimen, the EAG clinical experts did not consider this difference to have any bearing on the clinical, or safety results.

HRQoL outcomes for the expansion 4L+ subgroup were presented in the CS, while data for the 3L+ subgroup were only available in the CSR. No HRQoL data was presented for the optimisation cohorts. The EAG notes that changes generally did not exceed the MID.

The EAG considers it difficult to fully ascertain the generalisability of the EPCORE NHL-1 study to UK clinical practice in patients with FL. In part, this is due to the small sample size; however, the EAG notes that there are some differences in the sample from the UK only and the wider sample which may indicate some generalisability issues. Despite this, however, the EAG clinical experts did not have major concerns

with the representativeness of the EPCORE NHL-1 participants to the populations seen in UK clinical practice.

4 COST EFFECTIVENESS

4.1 *EAG comment on company's review of cost-effectiveness evidence*

The company undertook SLRs to identify cost-effectiveness studies, health-related quality of life (HRQoL) studies and cost and healthcare resource data in patients with R/R FL in a second-line or later setting. These are reported in Appendices E, F and G respectively of the CS. Searches for the cost-effectiveness and costs/healthcare resource use SLRs were undertaken together.

4.1.1 Search strategies

Searches were originally undertaken in April 2023, with updates in February and November 2024. An appropriate selection of sources was searched, including bibliographic databases, HTA agencies' websites and recent conference proceedings. Given that the CRD databases are no longer updated, the EAG would recommend searching the International HTA Database provided by INAHTA to ensure comprehensiveness and currency. Reference lists of previous SLRs, pooled analyses and meta-analyses were also checked (Appendices F and G, Tables 43 and 52), though reference lists of included studies do not appear to have been checked for additional studies.

The EconLit, Embase and MEDLINE search strategies (reported in Appendix E Tables 23-25, Appendix F Tables 39-41 and Clarification C8 Appendix 'Economic SLR search strategies') use multiple search terms for relapsed/refractory or 2L+ follicular lymphoma. In Embase and MEDLINE, these were combined with a comprehensive selection of Emtree/MeSH terms and free-text keywords relating to economic evaluations, cost effectiveness, HRQoL, costs and resource use.

Publication date limits have been used in update search strategies to exclude results published before the date of the previous search. This is not best practice and risks missing relevant results, as publications are not added to bibliographic databases as soon as they are published. More appropriate date fields such as "date created" or "date delivered" can be used for a comprehensive search. Additional limitations affecting the sensitivity of the search strategies include missing Emtree or MeSH headings for the relapsed/refractory concept ('refractory cancer', 'cancer

recurrence', 'salvage therapy', 'recurrence') and not searching the keywords field (using title and abstract fields only for free text searches).

The EAG ran targeted searches in MEDLINE and Embase (see Appendix 8.1.1 for search strategies) to check for any studies relevant to the NICE scope that may have been missed by the company's searches, whether due to limitations in the search strategies or because they were published in recent months. These searches identified no additional, relevant studies

4.2 *Summary and critique of the company's submitted economic evaluation by the EAG*

The eligibility criteria were suitable for the SLR performed. The results of the SLR appear comprehensive enough despite the limitations highlighted above. As the EAG's targeted searches failed to yield additional relevant data, the EAG considers the submitted economic evaluation evidence by the company comprehensive.

4.2.1 NICE reference case checklist

The EAG assessment against the NICE reference case checklist is presented in Table 24.

Table 24: NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Yes
Perspective on costs	NHS and PSS	Yes
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Yes

Element of health technology assessment	Reference case	EAG comment on company's submission
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes – 35.2 years
Synthesis of evidence on health effects	Based on systematic review	Yes
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	Yes
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Yes
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Yes (UK-specific tariffs were applied to the EQ-5D-3L EPCORE NHL-1 data to obtain the UK-specific utilities)
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Yes
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Yes
PSS, personal social services; QALYs, quality-adjusted life years; EQ-5D, EuroQol-5 dimension-3levels.		

4.2.2 Model structure

The company constructed a de novo cost-utility model with a weekly cycle length and a 35.2-year time horizon, using partitioned survival, to assess the cost-effectiveness of epcoritamab versus current 4L+ care. Three health states -

progression free (PF), progressed disease (PD), and death are described by the model (Figure 4).

All patients started in the PF state and remained there until disease progression or death. Patients whose disease progressed remain in the PD state until death (absorbing health state).

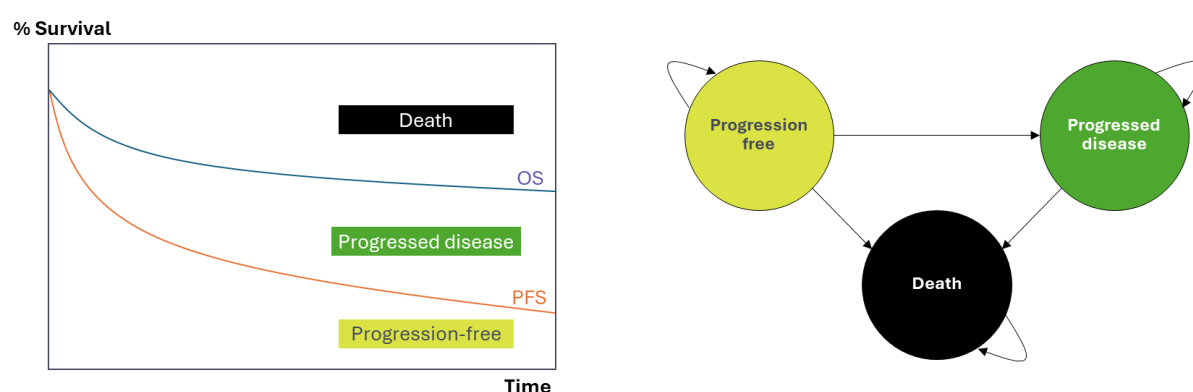


Figure 4: Partition survival model (PSM) and survival curves informing the proportion of patients per health state (OS, overall survival; PFS, progression free survival)

Source: CS Figure 21

The partitioned survival model (PSM) method uses “area under the curve” approach, where health state occupancy at a given time point is taken directly from survival curves fitted to the clinical data. The PFS curves, indicate, at each timepoint, the proportion of patients alive without disease progression whilst the OS curves represent proportion of patients alive at any given timepoint. The proportion of patients in the PD state was calculated as the difference between the proportion of living patients (OS health state) and the proportion of patients who are both living and pre-progression (PFS health state). The OS and PFS curves were determined by fitting parametric models to the EPCORE NHL-1 study data adjusted to the HMRN dataset through a MAIC analysis. MAIC-adjusted hazard ratios were applied to the unadjusted epcoritamab data to obtain the PFS and OS outcomes for the current 4L+ care (see section 4.2.6 for details).

Background mortality was used in the survival extrapolations in the model to ensure that the OS of patients does not exceed the survival of an age and sex matched population within the UK.

TTD for epcoritamab was assumed not equal to PFS in the base case analysis. Patients stopped treatment due to progression or other reasons with a stopping rule of 3 years applied to complete responders. Clinical experts to the EAG indicated it's reasonable to consider stopping point because of AEs that could occur at this time the longer patients are on treatment. The EAG therefore considers it a logical approach as consideration is given to treatment discontinuations prior to disease progression for reasons such as toxicity. For the comparator arm (current 4L + care), TTD was obtained directly from the HMRN raw data reflecting the impact of the varied fixed treatment durations of the therapies within the basket on cost-effectiveness outcomes.

The company did not apply treatment waning in the model. The EAG's clinical experts indicated that, when considering the population studied as a whole, one would expect that treatment does wane. One of the EAG's experts stated that "*the duration of complete responses curves do go down with time with just over 50% of the population who achieve CR remaining alive and in CR 3 years after achieving CR.*"

EAG Comments:

- A PSM is widely used in oncology trials to model clinically important endpoints such as OS and PFS and is suitable for use in this appraisal. Whilst the company's justifications for using a PSM appear reasonable the EAG believes the company should have considered a state transition model (STM) since they used complete response (CR) to adjust for PFS status (as seen in the estimation of utilities). This modelling approach would enable the transition of patients between sub-states (PFS with CR, PFS without CR, PD, and death), a proper estimation of proportion of patients with and without CR, the duration in CR/no CR in each model cycle and the associated outcomes.
- The lifetime horizon of 35.2 years, considering the mean age (64.80) of patients in the EPCORE NHL-1 trial at enrolment, is long enough to capture differences in costs and benefits associated with the strategies being compared.

- A weekly cycle length used in the model was short enough to accurately capture the model outcomes.
- TTD for epcoritamab was capped to PFS and OS to maintain consistency in the model. For the current 4L+, TTD was not capped but the EAG notes that the TTD curve was consistently below the PFS and OS over the modelled time on treatment.
- Treatment waning was not applied to the company's base case analysis or explored in scenario analysis. EAG's clinical experts' opinion is that treatment waning would occur and applying treatment waning in the economic model is a reasonable assumption. The EAG was unable to incorporate any treatment waning scenarios at the time of report submission as we awaited further input on clinically plausible treatment waning assumptions to explore.

4.2.3 Population

The economic model considered adult patients with R/R FL after three or more lines of systemic therapy, i.e., 4L+ R/R FL 1-3A patient population. As discussed in section 1.3, the population partially aligns with the NICE scope and the UK marketing authorisation (MA) for epcoritamab. The anticipated MA is for adult patients with R/R FL after two or more lines of systemic therapy (i.e. R/R 3L+ FL).

The base line characteristics of patients were informed by the EPCORE NHL-1 study's expansion cohort (n=81), a subset with R/R iNHL who have received three or more prior lines of systemic therapy (4L+). The EPCORE NHL-1 was an open label, phase 1/2, multicentre, multi-national single arm study evaluating dosage, efficacy and safety of epcoritamab in various forms of non-Hodgkin lymphoma (FL, DLBCL, and MCL). The trial was performed in three parts: dose escalation, dose expansion and dose optimization (see CS, section 2.3). The dose expansion FL cohort were made up of 3L+ FL population who had received 2 or more lines (n=128) with 81 at 4L+ with the primary outcome being ORR. As mentioned above, the model considered the R/R FL patient population that had received three or more lines of systemic therapy.

- The EAG considers that the 3L+ FL (n=128) broader population aligns better to the MA and NICE scope.

The baseline characteristics used in the cost effectiveness model (CEM) are mean age 64.80kg, gender distribution 34.6% female, mean weight 77.40kg and BSA 1.90m². Baseline mean age and gender distribution were used to obtain age and sex specific mortality for the general population. All doses in the model that are weight and body surface area (BSA) dependant were adjusted using the mean weight and BSA respectively

- The EAG's clinical experts indicated that baseline characteristics used in the economic model are reflective of the patient population seen in NHS clinical practice.

4.2.4 Interventions and comparators

4.2.4.1 Intervention

The intervention in this appraisal is epcoritamab. Epcoritamab is administered as a subcutaneous injection until disease progression, toxicity or withdrawal of consent. Whilst all efficacy analyses are based on the dose expansion cohort, the dosing data for epcoritamab used in the economic model is consistent with the optimisation part of the EPCORE NHL-1 trial for cycle 1. This was a priming dose of 0.16mg in day 1 cycle 1, two intermediate doses on day 8 (0.8mg) and day15 (3mg) of cycle 1 and full dose (48mg) on day 22 of cycle 1 and then weekly until the end of cycle 3. The full dose (48mg) is administered every two weeks in cycles 4-9 and every four weeks in cycle 10 and beyond (a cycle is 28days). In response to clarification A10, the company noted that the dosing in the optimisation part of the EPCORE NHL-1 reflects the anticipated UK MA and this step-up dosing had been explored in the optimisation part to reduce incidence of CRS. The company noted that pharmacokinetic outcomes had remained similar between patients who received the three step-up dose regimen and patients who received the two step-up dose regimens in EPCORE NHL-1. The EAG's clinical experts confirmed that the dose differences do not affect interpretation of results as the second intermediate dose (3mg on day 15) was given to mitigate AE of CRS.

- The EAG is satisfied with the dosing schedule used in the model for epcoritamab.

4.2.4.2 Comparators

The company modelled the comparator through a basket of care noting that there is no standard of care for patients with R/R FL 4L+ in UK clinical practice and treatments for these patients are individualised. The most prevalent option in each sub-basket as identified from the HMRN data was used to represent each sub-basket. For example, in the R-chemotherapy sub-basket, █% of patients received R-bendamustine, followed by R-CHOP (█%) and R-GDP (█%), the company chose R-bendamustine to represent the sub-basket in the current 4L+ care basket (Figure 5). In other + experimental sub-basket, obinutuzumab + bendamustine was selected to reflect UK clinical practice. A summary of the selected therapies used to represent each sub-basket is presented in Table 25

Clinical advice to the EAG also indicated no standard care for 4L+ and that treatments are based on whatever worked previously. Also, as new treatments get approved, treatment options start being used at earlier lines. As a result, best supportive care (BSC) would be an appropriate comparator as it is being considered in most 4L+ setting primarily due to lack of effective treatments for 4L+ patients.

The company has not considered best supportive care as a comparator as included in NICE scope because it is expected that patients who would receive BSC would not be considered fit enough to be eligible for an active intervention such as epcoritamab. Clinical advice to the EAG indicates BSC should be a comparator because some patients at 4L+ who are not fit enough for chemotherapy would be eligible for therapy with epcoritamab instead of BSC.

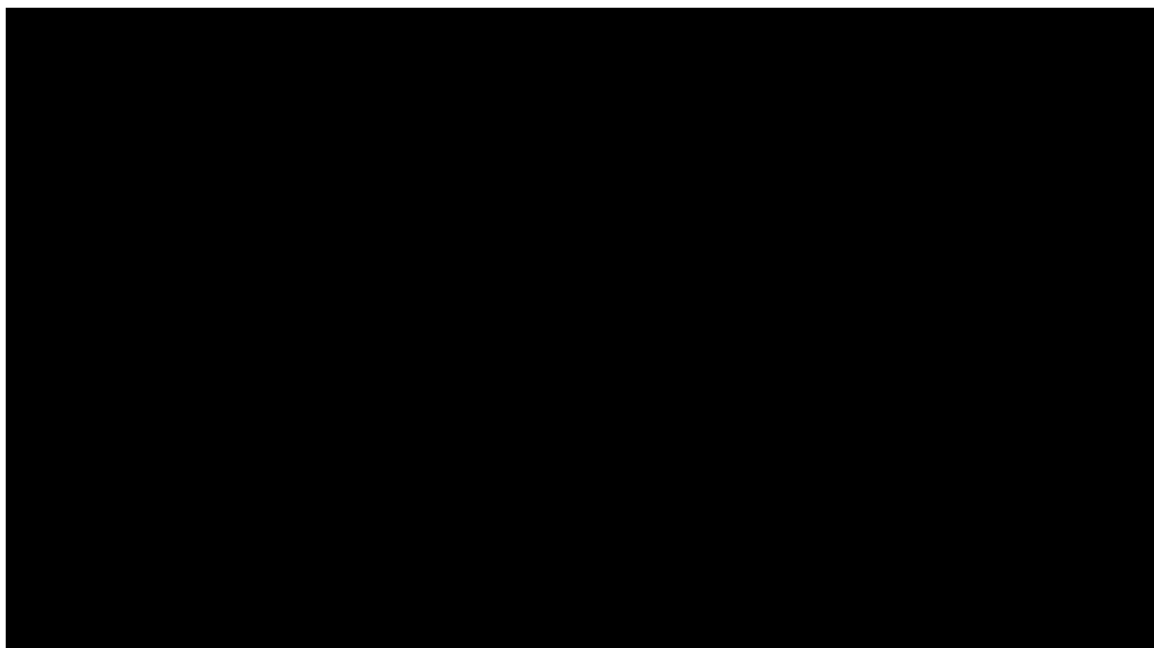


Figure 5: Approach of modelling the current 4L+ care basket using HMRN data. Source: CS figure 22.

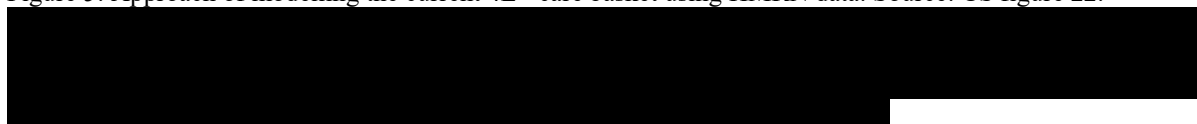


Table 25: Current 4L+ care basket of care for R/R FL used in the model

Sub-basket	Option	Share
Rituximab-chemotherapy	R-benda	%
Chemotherapy	chlorambucil	%
R ²	R ²	%
Other + experimental	Obinutuzumab + bendamustine	%

Source: Table 22, CS

R², rituximab + lenalidomide; R-benda, rituximab + bendamustine

4.2.5 Perspective and discounting

NHS and PSS perspective was used for estimating resource use and costs with an annual 3.5% discount rate applied to all costs and utilities in the model base case in line with NICE reference case.

4.2.6 Treatment effectiveness and extrapolation

To inform the health-state occupancy of the economic model, the company fitted parametric models to data from EPCORE NHL-1 to predict the future efficacy of epcoritamab PFS and OS, and applied hazard ratios from the MAIC analysis to predict the relative efficacy for the comparator group.

The company submission states that the overall survival modelling is described as incorporating background mortality by not permitting the modelled hazard rate to fall below the age and sex matched population of the UK. The EAG notes that the implementation of background mortality in the model does not exactly match this description and instead represents a relative survival approach where the impact of background mortality is applied in addition to trial mortality via an internal additive approach.

4.2.6.1 Epcoritamab

4.2.6.1.1 PFS and OS

For PFS and OS, the company fitted parametric survival models (exponential, Weibull, log-normal, log-logistic, Gompertz, and generalised gamma) to the COVID-modified dose-expansion 4L+ cohort PFS, OS, and TTD data from EPCORE NHL-1 (n=81), in line with NICE TSD14. Based on assessment of clinical plausibility and goodness-of-fit statistics, the company selects the log-normal extrapolation for both PFS and OS.

The EAG is content with the choice of PFS curve, however the OS extrapolation was deemed optimistic by the EAG clinical experts. If maintaining the use of the COVID-modified data, the EAG prefers to use the exponential extrapolation as it has the lowest goodness-of-fit statistics and produced the most pessimistic extrapolation of the models fitted to this data. The limited amount of information in the data owing to the limited sample size and number of events also aligns with selecting an extrapolation with fewer parameters being less prone to overfitting.

However, the EAG preference is to use the COVID-unmodified data from EPCORE NHL-1 for PFS and OS. Firstly, the EAG considers the extrapolations coming from the COVID-censored data to be too optimistic based on feedback from the EAG clinical experts. Secondly, the EAG is concerned about the potential for COVID to have affected the HMRN cohort and so should be maintained in the EPCORE NHL-1

data for balance. Thirdly, it is unclear whether COVID is solely attributable for all COVID-related death events. Following the same approach as the company, but using the COVID-unmodified data, the EAG also selects log-normal extrapolations for both outcomes.

The company consulted four clinical experts who provided predictions of future PFS and OS for epcoritamab. No estimates were shared with the EAG for the comparator population. The EAG is unclear over the context these estimates were generated in (i.e. what data were presented to the experts and whether it was specific to COVID-censored EPCORE NHL-1 population, or to UK real-world use of epcoritamab). The EAG's clinical experts commented that these predictions were optimistic for UK real-world population given the comorbidities and older age of this population, and uncertainty around long-term efficacy. The mid-values reported by the company were considered an upper bound by the EAG experts. The EAG notes that for 15 years and beyond, the company's OS extrapolations exceed the estimates of their experts.

Hence, the EAG is satisfied that their extrapolations using the COVID-unadjusted data result in less optimistic outcomes for epcoritamab, consistent with the expectations of their clinical experts.

Table 26: Comparison of EAG and Company preferred extrapolations for epcoritamab

	Company Expert PFS Preferred Value	Company Expert OS Preferred Value	Company PFS	Company OS	EAG PFS	EAG OS
3-year						
5-year						
10-year						
15-year						
20-year						

A visual comparison of the company and EAG preferred data and extrapolations is shown in Figure 5.

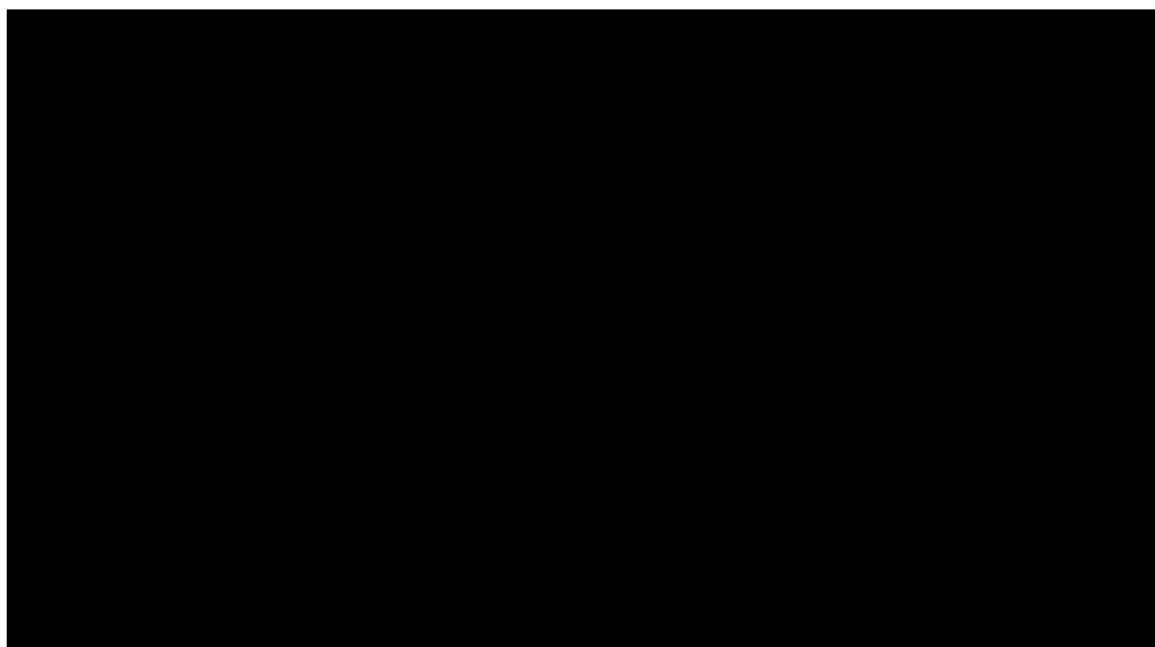


Figure 5: Company and EAG preferred epcoritamab PFS and OS extrapolations

The EAG also explored the impact of applying the MAIC hazard ratios to the parametric extrapolation of the HMRN data, to estimate the efficacy of epcoritamab. The QALYs are shown in an EAG scenario analysis. This resulted in very optimistic extrapolations for epcoritamab, which the EAG deem implausible and further evidence of the unsuitability of the MAIC.

4.2.6.1.2 TTD

The EAG considers the company's approach to TTD extrapolation, the choice of the log-normal, to be reasonable. Given that TTD was capped at three years in the model, any uncertainty beyond this point is unlikely to meaningfully impact the results.

4.2.6.2 Comparator

4.2.6.2.1 PFS and OS

For the comparator, the company apply hazard ratios obtained from their preferred MAIC and apply these to their preferred PFS and OS extrapolations for epcoritamab. This approach assumes that the hazard rates are proportional for the full duration of

economic model, as no waning effect is applied. The EAG was content that this assumption holds within the period we have follow-up for, but it is uncertain whether it is appropriate to maintain this assumption into the future. The hazard benefit is only reduced once background mortality comes into effect.

The EAG prefers to directly extrapolate the HMRN dataset due to the concerns with the MAIC. The EAG's preferred extrapolation is a log-normal model for both PFS and OS, which had the lowest goodness-of-fit statistics and good visual fit.

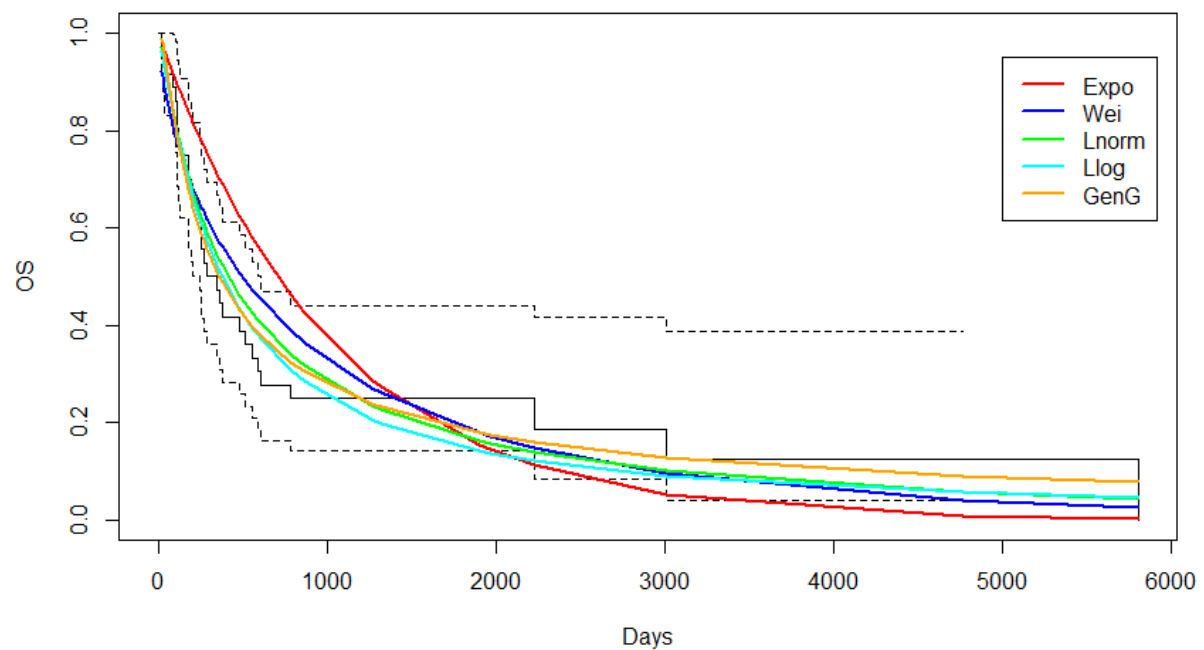


Figure 6: Overall survival extrapolations fitted to HMRN data

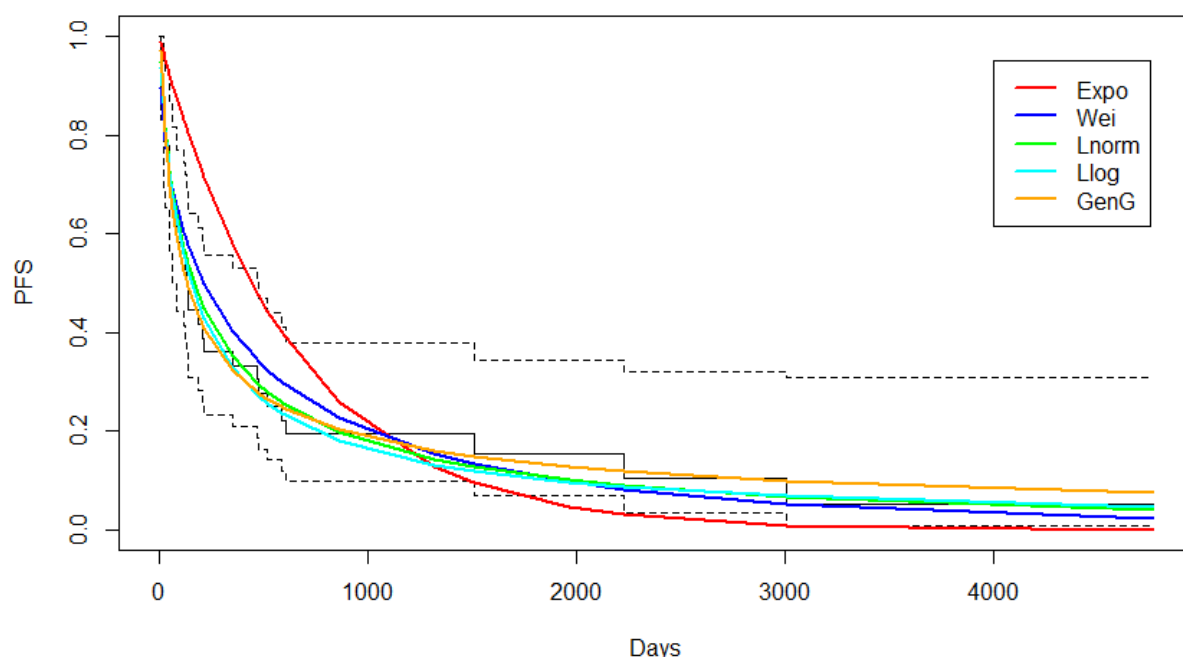


Figure 7: Progression-free survival extrapolations fitted to HMRN data

The resulting estimates of 3-year survival from the company's approach is noticeably below what was observed from the HMRN follow-up (PFS = ~█%; OS = ~█%), although the EAG accepts that the uncertainty in the data is high due to the small number of people contributing information at this stage. The EAG preferred approach to extrapolating HMRN data directly is a much better representation.

Table 27: Comparison of EAG and Company preferred extrapolations for the comparator

	HMRN PFS	HMRN OS	Company PFS	Company OS	EAG PFS	EAG OS
3-year	█	█	█	█	█	█
5-year	█	█	█	█	█	█
10-year	█	█	█	█	█	█
15-year	-	█	█	█	█	█
20-year	-	█	█	█	█	█

4.2.6.2.2 TTD

The EAG accepts the approach to extrapolation of HMRN TTD data, which fits an exponential model to the HMRN data, and does not consider any alternatives. Note, that time on treatment for the comparator is not capped.

The only EAG comment is to note an inconsistency between the data underlying TTD compared with PFS and OS. The company's approach to modelling TTD uses the HMRN data, whilst PFS and OS apply hazard ratios to extrapolations of EPCORE NHL-1 data, and so are not based on the same population. It is possible that efficacy and time on treatment will differ across these populations.

4.2.6.3 Additional EAG comments on time-to-event modelling

Whilst the EAG does not object to the selection process of the company's individual models, the EAG notes that the combination of models preferred by the company has some unexpected results. Firstly the post-progression survival for epcoritamab exceeds the pre-progression survival time for epcoritamab. Secondly, the mean post-progression survival for epcoritamab is far in excess of the equivalent time for current 4L+ care. Under the EAG's preferred approach to modelling, the epcoritamab post-progression survival time is less than the pre-progression survival time, and more similar to the comparator.

Table 28: Comparison of company and EAG mean time spent in each health state

	Mean Pre-Progression Survival	Mean Post-Progression Survival	Mean Overall Survival
Company - Comparator			
EAG - Comparator			
Company - Epcoritamab			
EAG - Epcoritamab			

4.2.7 Health related quality of life

4.2.7.1 Health-related quality of life data identified in the review

A SLR was conducted to identify HRQoL studies from electronic data bases as discussed in section 3.1. The search identified nine studies from 11 publications that included data for 2L+ R/R FL of which two reported patients receiving 3L+ therapy, three studies with data for R/R NHL: two reporting results of mixed population (> 80% FL) and one for a subset of FL.

The most used instrument to assess the HRQoL in the included studies is EORTC QLQ-C30 (n=5). Other instruments used are SF-36 (n=3), EQ-5D (n=3), and Functional Assessment of cancer Treatment-Lymphoma (FACT-Lym) (n=3).

Searches of previous NICE HTAs were also performed to identify and compare utility values used across the different appraisals. Utility values used for PFS were seen to be comparable.

The company selected the studies by Wild et al³⁷ and Cognet et al³⁸ from those identified in the SLR for their analysis. The utility decrement applied to the PFS to obtain the PD utility was based on Wild et al, 2006,³⁷ following precedents set in other FL NICE appraisals. Although this study is frequently used in NICE TAs of FL, it is still a conference abstract with no full text available. Utilities from Cognet et al³⁸ and TA892³⁹ were applied in scenario analysis but no justification provided for their preference.

EAG additional search did not find any relevant study.

4.2.7.2 Health related quality of life (HRQoL) obtained from clinical trial.

The primary source of HRQoL is the EQ-5D-3L obtained from patients in the (EPCORE NHL-1) study. A total of ■ complete measurements were obtained, ■ in the PFS and ■ in PD health state. The EQ-5D-3L questionnaires were completed in day 1 of cycles 1, 3, 5, 7 and 9 (treatment cycle is 28 days) and the last

measurement at the end of treatment, within 7 days of stopping treatment either due to disease progression or intolerable toxicities. The company notes a decrease in the number of completed questionnaires overtime (see CS section 3.4.1).

The EAG noted an error in the table reporting the number of observations. At clarification (question B1), the company corrected and presented an updated table. Table 29 shows the updated number of responses obtained from the trial by time point and health state.

Table 29: Number of responses in the FL 4L + population by time point and health state using the 23 April 2024 DCO (updated)

Time point	Number at risk*	Total observations	PFS	PD
Baseline:	■	■	■	■
Day 1 cycle 1	■	■	■	■
Day 1 cycle 3	■	■	■	■
Day 1 cycle 5	■	■	■	■
Day 1 cycle 7	■	■	■	■
Day 1 cycle 9	■	■	■	■
End of treatment	■	■	■	■

Source: CS Table 59. Number of patients receiving treatment at Day 1/3/5/7/9; FL, follicular lymphoma; DCO, data cut-off; PFS, progression free state; PD, progressed disease

The mean utility per health state (Table 30) indicates that patients had higher utility values when in the PD state. This result seems to be counter intuitive as patients were expected to have poorer prognosis as their disease progresses. The company notes the increase in utility observed in the PFS overtime can be attributed to the therapeutic effect such as Improved complete response (CR) and reduction in the disease burden which was also attributed to the higher utility recorded at the first measurement in the PD state immediately after stopping treatment. They further noted that initial PD measurement might reflect a period when patients experience alleviation of their symptoms, hence having higher utilities. Another factor that was associated with the counterintuitive result was the small number of observations recorded in the PD state which did not capture the long-time decline in disease status.

Table 30: Mean utility values obtained from the EPCORE NHL-1 trial data

Health State	Total observations	Unique subjects	Mean utility (SD)
PFS (baseline measurement)	■	■	■

PFS (all measurement)	■	■	■
PD (first measurement)	■	■	■
PD (all measurement)	■	■	■

Source: CS Table 60. SD, standard deviation; PFS, progression free state; PD, progressed disease

The CS stated a linear mixed model (LMM) that accounted for PFS/PD health states was performed on the utility data after applying UK -specific tariffs. The intercept and the health state coefficients obtained were 0.800 and 0.019 respectively with an insignificant p-value of 0.546. An estimated utility value of 0.800 for PFS and 0.819 for PD (Table 31) were obtained. The company appropriately concluded that the results of the LMM lacked face validity as PD utilities were greater PFS utilities, which is counterintuitive

During clarification, the company was asked to provide the list of covariates included in the LMM as well as the output from the regression (question B4). In their response, the company stated that they performed a LMM analysis on a subset of patients in the PFS which explored CR status. This is contrary to the information that was originally provided to the EAG in the CS concerning the LMM they performed. No regression output was provided for the LMM provided in the CS initially nor for the one in their response and the EAG was unable to validate the mixed model.

Table 31: Utility values per health state obtained from the company linear mixed model coefficients

Health state	Health state utility value
PFS	0.800
PD	0.819

PFS, progression free state; PD, progressed disease

4.2.7.3 Utilities by complete response status in the PFS health state

The company stated that advice from their clinical experts was that patients who achieved CR will have higher utility than those who do not. Based on that advice, an adjusted utility for the PFS was estimated for Epcoritamab and comparator arm that accounted for proportion of patients who achieved complete response (CR). In order to estimate the utility values in the PFS state for those who achieved a CR (at least

once) vs. those who did not achieve CR, the company first divided the patients from EPCORE NHL-1 study into two groups: PF with CR and PF without CR (see Table 32). A weighted utility was then derived for PFS based on the proportion of patients that have CR and no CR for both epcoritamab and the current 4L+ care (Table 33).

Table 32: Utility values in the progression-free state by CR status (from trial data)

Health state	Total observations	Unique subjects	Mean utility
PF with CR	195	46	0.832
PF without CR	61	35	0.736

Source: Table 64, CS

Source: CS Table 64. CR, complete response; PF, progression free

Table 33: Weighted PF utility by CR status

Therapy	PF with CR		PF without CR		Weighted PF utility
	Mean utility	Proportion achieving CR	Mean utility	Proportion not achieving CR	
Epcoritamab	■	■	■	■	■
Current 4L+ care		■		■	■

Source: CS Table 65

The utility for the PD state was obtained by applying a utility decrement of -0.187 sourced from Wild et al.2006³⁷ to the lower PF utility (PFS utility for current 4L+ care arm) which resulted in a utility of ■ for the PD state. A summary of the utility values used in the PFS and PD state in the company base case analysis are provided in Table 34. Utilities were adjusted by age and sex to account for decline over the model time horizon using the UK index of health state utility decline in Ara and Brazier.⁴⁰⁻⁴²

The company notes the utility in Wild et al have been applied in several NICE appraisals of R/R FL and the utilities used for PD state and PFS in the model base case are similar to utilities reported in published literature and previous HTAs.

Several scenario analyses were conducted by the company using different PFS and PD utility values obtained from previous HTAs and literature (details of this can be found in section 4.2).

Table 34: Utility values applied in the base case

Health state	Utility	Reference
PFS (epcoritamab)		EPCORE NHL-1 4L+ subgroup, HMRN and Wild et al .2006
PFS (current 4L+)		
PD		

Source: CS Table 66. PFS, progression free state; PD, progressed disease; HMRN, haematology malignancy research network

EAG comments:

The concerns of the EAG are:

- Linear mixed model analysis: As highlighted in section 4.2.7.2, the company said they performed a LMM twice, the first one accounted for health state PFS/PD which they reported lacks face validity. The second LMM was conducted on a subset of patients in PFS exploring the covariate “CR status”. The EAG could not validate both analyses because the company failed to provide the requested LMM output (Clarification response B14).
 - The EAG understands from the result presented (CS, Table 64) that CR status was applied to obtain utilities by using mean estimates of the patients who had CR and no CR from the trial data. The results do not reflect LMM regression results as no intercept or coefficients were presented for any variable.
- Using CR to adjust for PFS utility for both arms: Whilst the EAG experts agree with the PF utility by CR as disease status is a determinant of HRQoL, they noted that the impact of TEAEs on HRQoL in the PFS should also be considered because patients who achieve CR remain on treatment for a longer period in the epcoritamab arm. The EAG considers this approach might have created a form of bias in favour of epcoritamab.
 - The EAG prefers to use the same PFS utility for both arms in their base case analysis. A utility of [REDACTED] obtained by the company from the trial data without using CR status was applied for the PFS for both arms and a utility decrement used by the company from Wild et al was applied to the PFS utility to obtain PD utility.

- **Exclusion of adverse events disutilities:** Utility decrements from AEs were not included in the CEM base case analysis, and no justification was provided. It is worth noting that there have been inconsistencies in the application of utility decrements from AEs across NICE STAs of lymphoma. Whilst some appraisals have considered the use of AE disutilities in their economic model like in TA627, others like TA502 have not included it because the utility captured using the EQ-5D instrument within the clinical trials already accounted for decrements due to occurrence of AEs. Across literature different approaches have been applied. Some authors are of the opinion that the utility values of disease states already reflected the impact of AEs.⁴³ NICE TSD 12⁴⁴ states that a clear justification should be provided for either inclusion or exclusion of disutilities for adverse events in decision-analytic models. Consequently, the EAG performed a scenario analysis including AE disutilities to the company's base case to ascertain the impact of their base case assumption. The result suggests a negligible increase to the ICER.

4.2.7.4 Adverse Events

Adverse events (AEs) of grade 3 or 4 that occurred in $\geq 5\%$ of patients were included in the economic model. The source of AEs for epcoritamab is the EPCORE NHL-1 dose expansion 4L+ cohort (n=81) and that of the comparator was sourced from TA894. The company notes lack of safety data for chemotherapy made it difficult to model AE outcomes through the basket of care. AE reported for R-CHOP in a previous NICE TA894 appraisal was used to represent the AE for the current 4L+ care basket because R-chemo was the second largest sub-basket in the current 4L+ care.

Table 35 presents the TEAEs that were applied in the model. AEs that were recorded in EPCORE NHL-1 and not reported for R-CHOP were set to zero.

Table 35: Proportion of patients with grade 3+ TEAEs for each treatment arm

Grade 3 or 4 TEAEs occurring in $\geq 5\%$	Epcoritamab	Current 4L+ care (TA894)

	(EPCORE NHL-1 Expansion part 4L+ cohort)	
Anaemia		4.50%
COVID-19		0.00%
COVID-19 pneumonia		0.00%
Leukopenia/Leukocytopenia		30.80%
Lymphopenia		0.00%
Neutropenia		90.30%
Neutrophil count decreased		0.00%
Pneumonia		0.00%

Source: CS Table 58. TEAEs, treatment emergent adverse events

At clarification, the EAG asked the company to justify not exploring alternative AEs in the comparator arm that account for the varying proportions of AEs occurring across different treatment regimens (question B6). The company presented scenarios for AE incidence sourced from clinical trials as reported in TA627⁴⁵ and TA894⁴⁶ for O-Benda (from GADOLIN),⁴⁷ R-CVP (from RELEVANCE)⁴⁸ and R² (from MAGNIFY)⁴⁹ instead of R-CHOP as in the base case which still does not reflect the varying proportions across the different treatments in the basket.

EAG comment:

- The EAG is concerned that the approach used by the company to assign AEs to the current 4L+ basket of care does not accurately capture the probabilities of AEs that represent the therapies in the basket. The EAG believes that using varying proportions across the different therapies in the basket to provide a weighted value for each AE will better represent the AEs for the current 4L + care arm which is consistent with a previous NICE TA1001 appraisal where HMRN therapy basket was also used as comparator. This approach has been applied in the EAG base case.
- Another area of uncertainty is the exclusion of CRS AE from the epcoritamab arm which would have underestimated the costs of AEs resulting from the use of epcoritamab. Though in the CS, CRS grade 3+ occurred in only one patient (1.2%) in the EPCORE NHL-1 study expansion phase (n=81), grade 2 CRS required treatment with tocilizumab and other care provided for CRS patients. The EAG believes epcoritamab use may lead to some patients, necessitating treatment with tocilizumab in practice and prefers that all grade 2 CRS

requiring treatment with tocilizumab be included in the CEM. This approach is consistent with previous NICE appraisal TA894 of R/R follicular lymphoma and has been included in the EAG base case.

4.2.8 Resources and costs

4.2.8.1 Resource use identification, measurement and valuation studies

The CS stated a SLR was performed to identify costs and resource use data that might be relevant to this appraisal. 16 studies were identified across 18 publications which included four retrospective studies that reported patients on 3L+ therapy. Fourteen studies reported on direct health care costs and resource use and no study reported any indirect costs.

- Direct costs reported across the studies are medical costs, inpatient costs, outpatient costs, emergency room (ER) costs, physician office visit costs, pharmacy costs and treatment costs specific to FL.
- Resource use reported are frequency of inpatient hospitalisation, ER visits, physician office visits, length of stay in hospital; inpatient and ICU, outpatient visits including number of days in outpatient services, and drug administration days.

No study was found that reported data for a UK population. The studies reported were for US (10), Canada (1), Italy (1), multiple location (1) and 3 did not have any geographical focus.

A detailed critique of the search strategy is provided in section 4.1. In the EAG additional search, no relevant study was identified.

4.2.8.2 Intervention and comparator costs

The main costs categories included in the CEM are as follows: Drug acquisition and administration costs for epcoritamab and the Current 4L+ care, subsequent

treatment costs, health care resource use and costs (including costs of disease progression and terminal care costs), and adverse event costs.

Epcoritamab acquisition and administration costs

The cost of epcoritamab for each model cycle (7 days) was made up of drug acquisition and administration costs. The dosing regimen for epcoritamab (Table 36) is consistent with the EPCORE NHL-1 optimization phase.

Table 36: Dosing regimen for Epcoritamab

Dose	Administration Frequency
0.16 mg	One administration on day 1 of cycle 1 (28-day cycle)
0.80 mg	One administration on day 8 of cycle 1 (28-day cycle)
3.00 mg	One administration on day 15 of cycle 1 (28-day cycle)
48.0 mg	Once weekly from day 22 of cycle 1 (28-day cycle) until cycle 3 Once every two weeks for cycle 4 to 9 Once every four weeks from cycle 10 and beyond

Source: CS Table 45

The unit cost for epcoritamab is £6,568 for 48mg and £547.33 for 4mg pack sizes which were sourced from the BNF.⁵⁰ A relative dose intensity of ■% was applied to the 48mg dose, while ■% was applied to the priming dose (0.16mg) and the two intermediate doses (0.80mg and 0.3mg). The PAS price was applied for epicoritamab 48mg (£■■■■), and 4mg (£■■■■) in the CEM and vial sharing was assumed in the base case analysis.

Epcoritamab costs were estimated throughout the time patients were on treatment according to the modelled TTD curve as discussed in section 3.2.5. In the model base case, patients continued treatment until disease progression or discontinuation due to toxicity or other reasons. A stopping rule of 3 years was applied for patients that achieved CR therefore costs of epcoritamab were no longer accrued after 3 years. A scenario analysis using 2 years stopping rule was explored to assess the impact of the stopping rule assumption.

Epcoritamab is administered subcutaneously. The unit administration cost (Table 37) was obtained from the NHS reference costs.⁵¹ The EAG had concerns with the

exclusion of costs associated with concomitant medications. At clarification (question B2), the company was asked to provide the rationale for exclusion of this treatment related costs. The company responded by including the costs of dexamethasone, antihistamine and antipyretic and provided an updated model that allows for inclusion or exclusion of costs of concomitant medications. The ICER obtained shows a minimal change to the company's base case ICER (■■■%). The EAG is satisfied with this approach.

Table 37: Epcoritamab administration cost

Route of administration	Costs	Reference
Subcutaneous	£133.39	SB12Z (NHS Reference costs 2023/24)

Source: CS Table 72

Current 4L+ care acquisition and administration costs.

In the CS, current 4L+ care was modelled through a weighted basket of care identified from HMRN.²⁹ The company states the approach was validated by UK clinical experts during engagement. The basket was costed using the dosing regimen of therapies that are most used within each sub basket in clinical practice. Table 38 shows composition of the therapies within each sub basket that were used to represent the current 4L+ care in the CEM.

The acquisition costs of each therapy in the sub basket per cycle was estimated using the dosing regimens (Table 40) and the maximum treatment durations as described in SmPC. The proportion of patients treated with each therapy was then used to calculate the weighted cost per cycle which was applied through the model cycle using the modelled TTD curve. The unit costs for the therapies within the basket were sourced from the BNF⁵² and eMIT⁵³ (Table 40) and vial sharing was not permitted in the base case analysis. The EAG requested clarification on why different assumptions on vial sharing were used in the CEM (question B3) for epcoritamab and the comparator. The company explained that for therapies where BSA is used to determine dosage, it might be difficult to keep to vial sharing as treatments tend to be more individualised than fixed doses. Thus, the assumption for drug wastage was considered for the current 4L + care arm. The company performed scenario analysis that assumed vial sharing for both arms and the result

shows that company base case ICER increased by █%. Clinical advice for EAG clarifies that vial sharing applies only to the 3-step up doses. Other (48mg) doses will use full vials, hence minimal impact on results.

In a scenario analysis, the company evaluated the costs of using different proportions for therapies in the current 4L+ care basket sourced from TA894. The proportions of which are R-chemotherapy (64.2%), chemotherapy (0%), R² (22.5%), and other immune-chemotherapies (13.3%). This resulted in a decrease in the ICER from the company base case by █%.

Table 38: Composition of current 4L+ care applied in the model

Sub-basket	Most prevalent treatment option	Proportion of basket (%)	Source
R-chemotherapy	Rituximab + bendamustine	█	HMRN
Chemotherapy	Chlorambucil	█	
R ²	Rituximab +lenalidomide	█	
Other immune-chemotherapy	Obinutuzumab +bendamustine	█	

Source: CS Table 68 & 71. R², rituximab + lenalidomide; HMRN, Haematology Malignancy Research Network; R-Chemotherapy, rituximab + chemotherapy

Table 39: Dosing regimen of current 4L+ care

Sub-basket	Therapy		Dose	Adminstration route	Dose regimen	Reference
R-Chemo	Rituximab + bendamustine	Bendamustine	90mg/m ²	IV	Cycles 1-6: Day 1 and 2 (28-day cycle)	NHS protocol ⁵⁴
		Rituximab	375mg/m ²	IV	Cycles 1-6: Day 1 (28-day cycle)	
Chemotherapy	Chlorambucil	chlorambucil	10mg	Oral	Cycles 1-6: Day 1-14 (28-day cycle)	Southwest Clinical Network ⁵⁵
R ²	Rituximab + lenalidomide	Rituximab	375mg/m ²	IV	Cycle 1: Day 1, 8, 15, 22	SmPC ⁵⁶

					(28-day cycle) Cycle 2-5: Day 1 (28-day cycle)	
		lenalidomide	20mg	Oral	Up to 12 cycles: Day 1-21 of 28-day cycles	
Other immunotherapies	Obinutuzumab + bendamustine	Obinutuzumab	1000mg	IV	Cycle 1: Day 1, 8, 15 (28-day cycle) Cycles 2-6: Day 1 (28-day cycle) Followed by maintenance every 2 months for 2 years or until disease progression	SmPC ⁵⁷
		Bendamustine	90mg/m ²	IV	Cycles 1-6: Day 1 and 2 (28-day cycle)	Southwest Clinical Network ⁵⁸

Source: CS Table 69. R-chemo, rituximab with chemotherapy; R², rituximab with lenalidomide; IV, intravenous; SmPC, summary of product characteristics

Table 40: Acquisition costs for current 4L + care

Treatment regimen	Drug	Dose	Costs per package	Source
R-chemotherapy	Rituximab	2 x 100mg	£314.33	BNF
		2 x 500mg	£1,571.67	
	Bendamustine	5 x 25mg	£40.86	eMIT
		1 x 100mg	£91.99	
		5 x 100mg	£127.14	
Chemotherapy	Chlorambucil	25 x 2mg	£11.00	BNF
R ²	Rituximab	2 x 100mg	£314.33	BNF
		2 x 500mg	£1,571.67	
	Lenalidomide	21 X 2.5mg	£26.23	eMIT
		21 X 5mg	£31.48	
		21 X 7.5mg	£45.16	
		21 X 10mg	£27.55	
		21 x 15mg	£30.76	
		21 x 20mg	£43.27	
		21 x 25mg	£28.27	
Other immunotherapies	Obinutuzumab	1 x 1000mg	£3,312.00	BNF
		5 x 25mg	£40.86	
	Bendamustine	1 x 200mg	£91.99	eMIT
		5 x 100mg	£127.14	

Source: CS Table 70. R², rituximab +lenalidomide; BNF, British National Formulary; eMIT, electronic market information tool

The administration costs were calculated for the duration of treatment for each 4L+ therapy in the basket. The total administration costs were then divided by the maximum time on treatment for each therapy to obtain the administration costs per cycle. The unit drug administration costs (Table 41) were sourced from the NHS reference costs 2023/24.

The company was advised by their experts who note that subcutaneous administration of epcoritamab offers advantages over the current intravenous route for 4L+ FL treatments. Drugs administered intravenously were assumed to incur a higher drug administration cost than epcoritamab administered subcutaneously, while no administration costs were associated with oral therapies. The EAG is satisfied with these assumptions.

Table 41: Drug administration costs for current 4L + care basket

Administration route	Costs	Reference
Intravenous (IV)	£198.08	SB15Z (NHS Reference costs 2023/24)
Oral	£0	Assumption

Source: CS Table 72

4.2.8.3 Costs of subsequent treatment

In the CEM, patients in both arms received subsequent treatments (i.e. $\geq 5^{\text{th}}$ line of therapy (LOT)) upon progression to the PD state. The treatments were assumed to be the same for both arms because there is no standard treatment pathway for those reaching 4L+. While the EAG were concerned with this assumption, advice from their clinical experts confirmed its rationality, due to the absence of a standard treatment for patients at 4L+ and typical recycling of prior treatments.

The costs of subsequent treatments were applied as a single costs per cycle throughout the time patients are in the PD state. These costs were estimated from the drug acquisition and administration costs of treatments within the basket based on their dosing schedules as defined by their SmPC divided by the number of cycles (time on treatment) for each therapy to obtain the average costs per cycle (Table 42). The average costs per cycle were weighted according to share of patients on each therapy to obtain the basket cost per cycle which was then applied throughout the cycle duration that patients remain in the PD state. All patients (100%) that progressed were assumed to receive subsequent treatment in the CEM. The EAG considers the assumptions used in estimating the costs of subsequent treatment to be appropriate.

The company explored the impact of changing the basket mix of subsequent treatment by using current 4L+ care basket proportions obtained from TA894 as outlined in section 4.2, Table 43.

Table 42: Subsequent treatment cost per cycle and time on treatment

Subsequent treatments	Time on treatment (weeks)	Average treatment acquisition costs per cycle	Average administration costs per cycle	Average costs per cycle
R-chemotherapy	21			
Chemotherapy	22			
R ²	47			
Other immune chemotherapies	101			

Source: CS Table 73. R-chemotherapy, rituximab +chemotherapy; R², rituximab +lenalidomide

4.2.8.4 Health state resource use and costs

Disease management costs were estimated as a product of resource use per cycle and the unit cost of each resource item and applied to each model cycle to patients that are alive. The costs were considered to differ by health state (PFS and PD) not by treatment arm. According to the CS, the health state resource use (Table 43) comprising of monitoring activities and procedures performed in each health state was based on previous TA892⁴⁶ and validated by clinicians.¹⁶

The unit cost for resource use were obtained from NHS reference costs 2023/24⁵¹ and TA892,⁴⁶ inflated to 2023/24.

Table 43: Resource use and unit costs

Activity	Frequency per cycle			Unit costs	Reference
	PFS	PD	Reference		
Haematologist led consultation	Once a month	Once a month	TA892 and clinical opinion	£204.32	NHS Reference Costs 2023-24 WF01A
Full blood count	Once a month	Once a month	TA892 and clinical opinion	£7.90	TA892 inflated using PSSRU 2022/2023
Full profile (U&E, LFT, calcium)	Once a month	Once a month	TA892 and clinical opinion	£21.52	TA892 inflated using PSSRU 2022/2023
Serum IgG, IgA, IgM and electrophoresis	Once a month	Once a month	TA892 and clinical opinion	£31.58	TA892 inflated using PSSRU 2022/2023
Lactate Dehydrogenate (LDH) test [†]	Once a month	None	TA892 and clinical opinion	£15.97	TA892 inflated using PSSRU 2022/2023
Computer tomography (CT) scans [†]	Once a year	None	TA892 and clinical opinion	£142.63	NHS Reference Costs 2023-24 RD27Z

Source: CS Table 74. LFT, lateral flow test; U&E, urea and electrolytes; Ig, immunoglobulin; PFS, progression free state; PD, progressed disease; PSSRU, personal and social services Research Unit

[†]Based on the ESMO FL guidelines, an LDH test and CT scan are only resourced when patients are in PFS⁵⁹

The costs of the LDH test were noted to be omitted in the CEM for PFS. This has been corrected and included in the EAG base case.

EAG clinical experts confirmed that the resource usage applied by the company are reasonable but notes the haematologist consultation in the first month is more frequent with epcoritamab as the infusions are done on a weekly basis and monthly thereafter. In addition, one of the experts indicated a PET scan every 6months-12months should be included. The EAG have performed scenario analyses to assess the impact of the additional resource use on the company's base case assumptions (see section 6.1).

Disease progression and Terminal care costs

When patients enter the PD state and death state, they were assumed to incur a cost on disease progression and terminal care respectively. These costs were applied as a one-off cost as patients enter the PD state and death state.

Table 44 presents the one-off cost applied in the model for patients that progress to PD state. All patients (100%) are assumed to undergo radiological assessment and blood tests with 25% receiving a biopsy. The CS mentioned this assumption is in line with TA892.

A terminal care costs of £7,363.85 was applied to any patient who entered the absorbing death state. The EAG is satisfied with these assumptions.

Table 44: Resource use and unit costs of disease progression

Activity	Disease progression	Unit costs	Reference
Radiological assessment	100%	£102.78	NHS Reference Costs 2023-24 RD20A
Biopsy	25%	£951.68	NHS Reference Costs 2023-24 SA33Z
Blood test	100%	£8.04	NHS Reference Costs 2023-24 DAPS05

Source: CS Table 75. NHS, national health service

4.2.8.5 Adverse events costs

Adverse events costs were applied as a one-off cost in the first cycle of the model, estimated as a product of the incidence of AEs and the unit cost of each AE. As discussed in section 4.2.7.4, the EAG had concerns with the company's approach of implementing AE costs for the current 4L+ comparator arm and the exclusion of CRS in the epcoritamab arm. This would have overestimated the costs of AEs for the comparator and underestimated AE costs for epcoritamab in the CEM.

The unit costs of AEs were sourced from the NHS reference costs 2023/24 (Table 45).

Table 45: Adverse events costs

Adverse Event	Cost	Reference
Anaemia	£5,305.01	National Schedule of Reference Costs 2023-24: weighted average of SA03G to SA03H
COVID-19	£2,108.52	National Schedule of Reference Costs 2023-24: DX21A
COVID-19 pneumonia	£2,897.93	National Schedule of Reference Costs 2023-24: DX11A
Leukopenia/leukocytopenia	£560.68	National Schedule of Reference Costs 2023-24: Weighted average of SA08G to SA08J
lymphopenia	£560.68	National Schedule of Reference Costs 2023-24: Weighted average of SA08G to SA08J
Neutropenia	£560.68	National Schedule of Reference Costs 2023-24: Weighted average of SA08G to SA08J
Neutrophil count decreased	£560.68	National Schedule of Reference Costs 2023-24: Weighted average of SA08G to SA08J
Pneumonia	£2,741.34	National Schedule of Reference Costs 2023-24: Weighted average of DZ23J:DZ23N

Source: CS Table 77

EAG comments:

The EAG deems the estimation of resource use and costs reasonable, but concerns included:

- Clinical benefits of subsequent treatments used in the EPCORE NHL-1 study captured without corresponding presentation of associated costs: The company assumed both arms received the same subsequent treatments for reasons highlighted in section 4.2.8.3. This assumption was validated by the company and the EAG experts as the subsequent treatments reflect UK clinical practice. Considering that in the EPCORE NHL-1 study the FL 4L + (n=81) patients received different subsequent treatments; systemic anti-lymphoma therapy (■■■%), allogenic stem cell transplant (■■■) and CAR-T therapy(■■■), the EAG is concerned that the effect of epcoritamab might have been overestimated in the clinical efficacy data used in the CEM for patients who were not censored (■■■ who received CAR-T). Not adjusting for treatment effects of the subsequent treatments received by these patients would have inherently biased the results of the analysis in favour of epcoritamab.
- Resource use in the epcoritamab arm: Resource use for haematologist consultation was thought to be underestimated for epcoritamab. EAG clinical expert advised that patients on epcoritamab will have weekly visits in the first month and then monthly visits thereafter. Also, the use of PET scan every 12 months. The EAG have considered the increased haematologist consultant visits in its base case and explored inclusion of PET scans in a scenario analysis.
- Adverse event costs in the epcoritamab arm: Adverse event costs were thought to be underestimated for epcoritamab because of exclusion of CRS which is a major AE associated with the use of epcoritamab. The EAG notes that in the EPCORE NHL-1 study, some patients who had grade 2 CRS were treated with tocilizumab. Therefore, EAG have added costs of all grades 2

CRS that required treatment with tocilizumab in the EPCORE NHL-1 trial expansion part (4L+) in their base case analysis.

4.2.9 Severity

The company quantified disease severity through two different but related measures of disease severity – the absolute QALY shortfall and proportional QALY shortfall - in line with NICE's Health Technology Evaluations manual.⁶⁰ Absolute shortfall represents the number of future QALYs that are lost by people living with the disease and *on current standard of care* whilst proportional shortfall represents the proportion of future QALYs that are lost by people living with the disease and *on current standard of care*. The severity modifier reflects a spectrum of disease severity and allows a QALY weight of (x1, x1.2 and x1.7) to apply depending on the QALY shortfall (AS or PS) (Table 46). The multiplier is applied to the incremental QALYs associated with a technology before the calculation of ICERs implying the £20,000 to £30,000 threshold is retained regardless of QALY weight chosen.

Table 46: QALY weightings for severity

QALY weight	Proportional QALY shortfall	Absolute QALY shortfall
1	Less than 0.85	Less than 12
X1.2	0.85 to 0.95	12 to 18
X1.7	At least 0.95	At least 18

The number of QALYs that the general population living without the condition would be expected to accrue for the rest of their lifetime was estimated to be 10.91 and was based on the characteristics of the EPCORE NHL-1 4L+ study subpopulation i.e., age = 64.80 years and proportion females = 34.60%. The remaining QALYs accrued by people with *relapsed or refractory follicular lymphoma after three or more systemic treatments* and on current standard of care were 0.985 and estimated using the company's base case cost-effectiveness model. The resulting QALY shortfalls (absolute and proportional) are shown in Table 47 below. Since the absolute QALY shortfall is below 12 but the proportional QALY shortfall greater than 85%, the company appropriately concluded that, based on their base case assumptions, a x1.2 multiplier for disease severity was appropriate for this appraisal as per NICE guidance.

Table 47: Summary of QALY shortfall analysis (table 59 CS)

Approach	Expected total QALYs for the general population	Total QALYs that people living with a condition would be expected to have with current treatment	Absolute QALY shortfall	Proportional QALY shortfall	QALY weight
Company	10.91	0.985	9.93	91%	x1.2
EAG	10.91	1.70	9.21	84.4%	x1

The EAG replicated the QALY shortfall analysis, but using the EAG's preferred base case assumptions in the economic model and arrived at a different conclusions. Based on the EAG's preferred assumptions, the remaining QALYs accrued by people with *relapsed or refractory follicular lymphoma after three or more systemic treatments* and on current standard of care are estimated to be 1.70 vs. 0.985 (company's). The proportional QALY shortfall was less than 85% (but very close i.e., 84.4%) whilst absolute QALY shortfall <12. Therefore, in its base case the EAG does not include a severity modifier, but presents EAG's base case ICER adjusted for x1.2 severity modifier in Table 55.

EAG comments:

- The company appropriately estimated the absolute and proportional QALY shortfalls, using preferred value sets.⁴⁰
- The EAG was able to replicate the QALY shortfall values in the company submission.
- The EAG recalculated the QALY shortfalls based on EAG's base case assumptions and arrived at different conclusions from the company's i.e., a severity weighting does not apply for this appraisal.
 - It is uncertain whether a severity modifier is appropriate for this appraisal.

5 COST EFFECTIVENESS RESULTS

5.1 *Company's cost effectiveness results*

Table 48 presents the discounted life years gained (LYG), quality adjusted life years (QALYs), total and incremental costs, between epcoritamab and current 4L+ care for the company's base case deterministic analysis. The base case analysis applied QALYs that had been adjusted for severity (section 6.1). The incremental QALYs and LYG were 7.018 and 3.994 respectively. The ICER of █████ fell below the £20,000 - £30,000/QALY thresholds. Generally, NICE considers technologies costing between £20,000 and £30,000 per additional QALY gained to represent good value for money for the NHS. The corresponding net monetary benefit (NMB) at £30,000/QALY was █████ whilst the net health benefit was █████. Without adjusting QALYs for severity, and using the same base case model assumptions, the resulting ICER of £████, also fell below the £30,000 willingness to pay threshold in the company's analysis.

Table 48: Deterministic base case cost-effectiveness results, epcoritamab vs. current 4L+ care: Epcoritamab PAS price

Technologies	Total				Incremental				ICER (£/QALY)
	Costs (£)	LYG	QALYs (severity unadjusted)	QALYs (severity adjusted)	Costs (£)	LYG	QALYs unadjusted	QALYs Adjusted	
Epcoritamab	████	8.758	4.313	5.176	-	-	-		-
Current 4L+ Care	████	1.740	0.985	1.182	████	7.018	3.328	3.994	████

5.2 *Company's sensitivity analyses*

Uncertainty was explored via probabilistic sensitivity analysis, scenario analyses and univariate sensitivity analyses.

In line with PSA methodology, each uncertain parameter in the model was represented as a probability distribution, based on published recommendations. One thousand simulations were performed for the PSA, allowing values to be drawn at

random from each probability distribution, for every simulation. Table 49 shows the results of the PSA for the analysis where QALYs are not adjusted for severity. The corresponding incremental cost-effectiveness scatterplot and cost-effectiveness acceptability curves are shown in Figure 8 and Figure 9. The scatterplot shows that the iterations fall within the [REDACTED] indicating that epcoritamab is [REDACTED] and [REDACTED] than current 4L+ care at a WTP threshold of £30,000 per QALY. The probability of cost-effectiveness at similar threshold was [REDACTED]%. It is worth noting that for the PSA, the company did not apply the severity modifier directly to the incremental QALYs but to the WTP threshold. The company justified this approach on the basis that “as the PSA samples each parameter individually according to their mean and standard error, the output of the analysis cannot robustly incorporate a severity modifier as variations in individual parameters may impact absolute and proportional QALY shortfall”. By applying the severity modifier (x1.2) to the £30,000/QALY WTP threshold, the company concludes that, probability of cost-effectiveness of epcoritamab is [REDACTED]% at the adjusted WTP threshold of £36,000/QALY. The NICE guidance is that the severity modifier should be applied to the incremental QALYs. However, whether the severity modifier was applied to incremental QALYs after PSA or the modifier was applied directly to WTP returns similar conclusions in company's base case.

Table 49. Probabilistic base case cost-effectiveness results, epcoritamab vs. current 4L+ care - epcoritamab PAS price

Technologies	Total		Incremental		
	Costs (£)	QALYs(unadjusted)	Costs (£)	QALYs (unadjusted)	ICER (£/QALY); unadjusted
Epcoritamab	[REDACTED]	4.404	-	-	-
Current 4L+ Care	[REDACTED]	1.066	[REDACTED]	3.338	[REDACTED]

Source: Table 83 CS; PSA analysis does not include a severity modifier

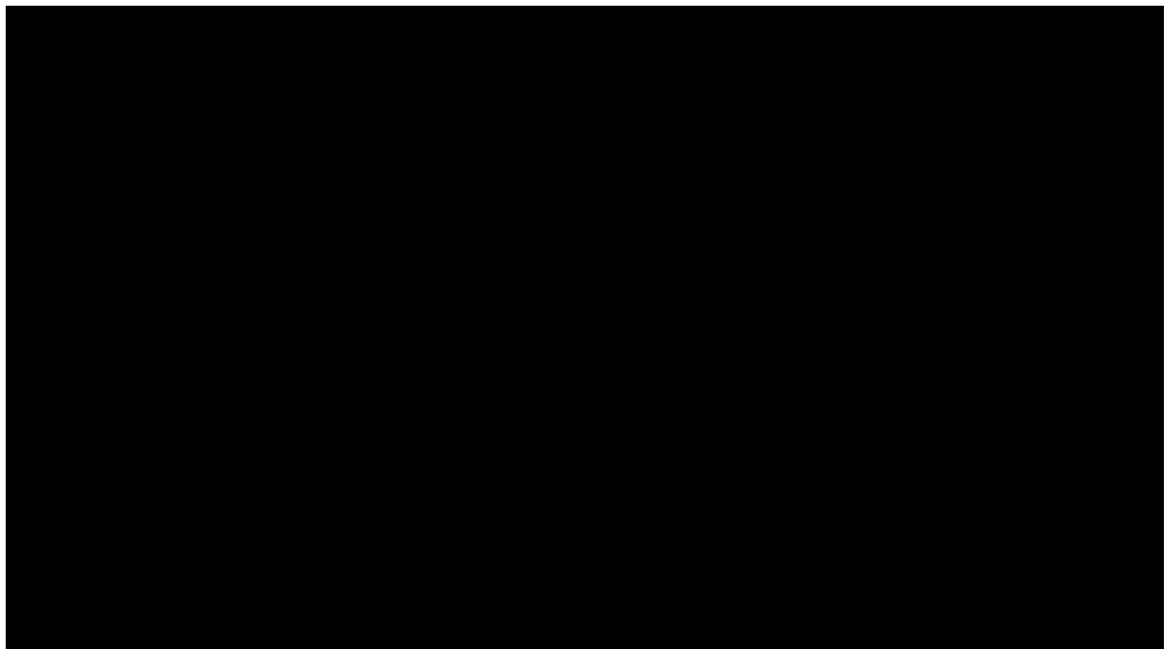


Figure 8: Cost-effectiveness scatterplot - incremental costs and QALYs of epcoritamab vs. current 4L+ care

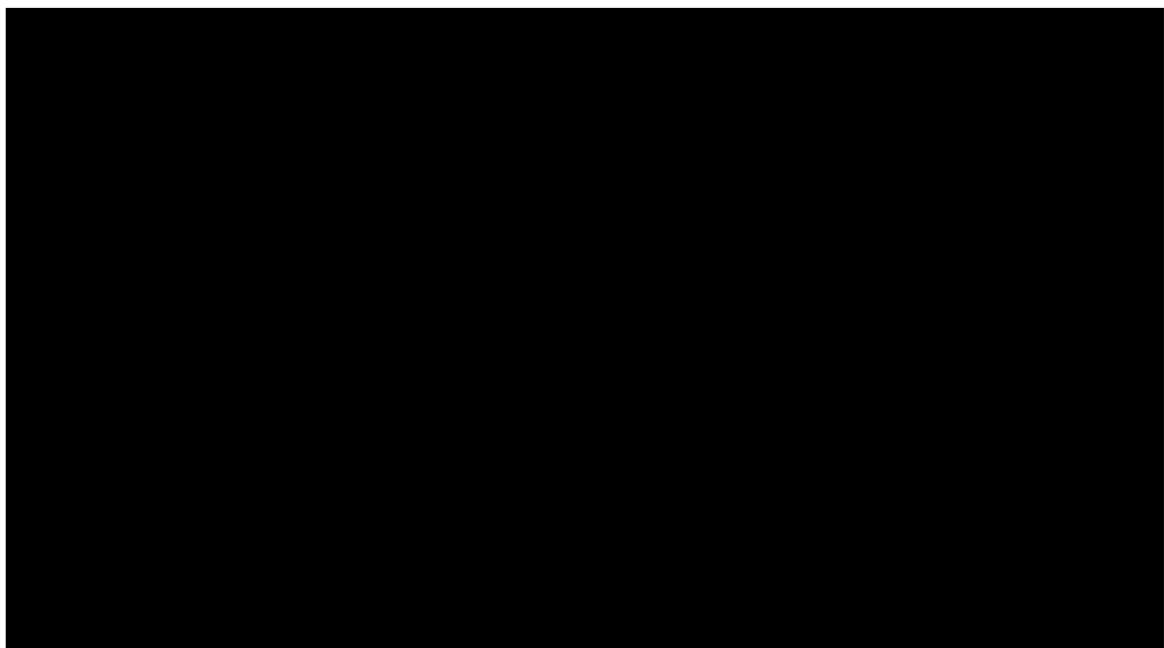


Figure 9. Cost-effectiveness acceptability curve - probability of cost-effectiveness, at different willingness to pay thresholds, of epcoritamab vs. current 4L+ care

Univariate sensitivity analysis was performed for a number of parameters in the model. The results were presented using a tornado diagram showing the 15 parameters that had the greatest impact on the ICER. HR for OS between

epcoritamab and current 4L+care was the key driver of uncertainty in both incremental costs and incremental QALYs, followed by PF utility value used in the base case analysis (Figure 10)

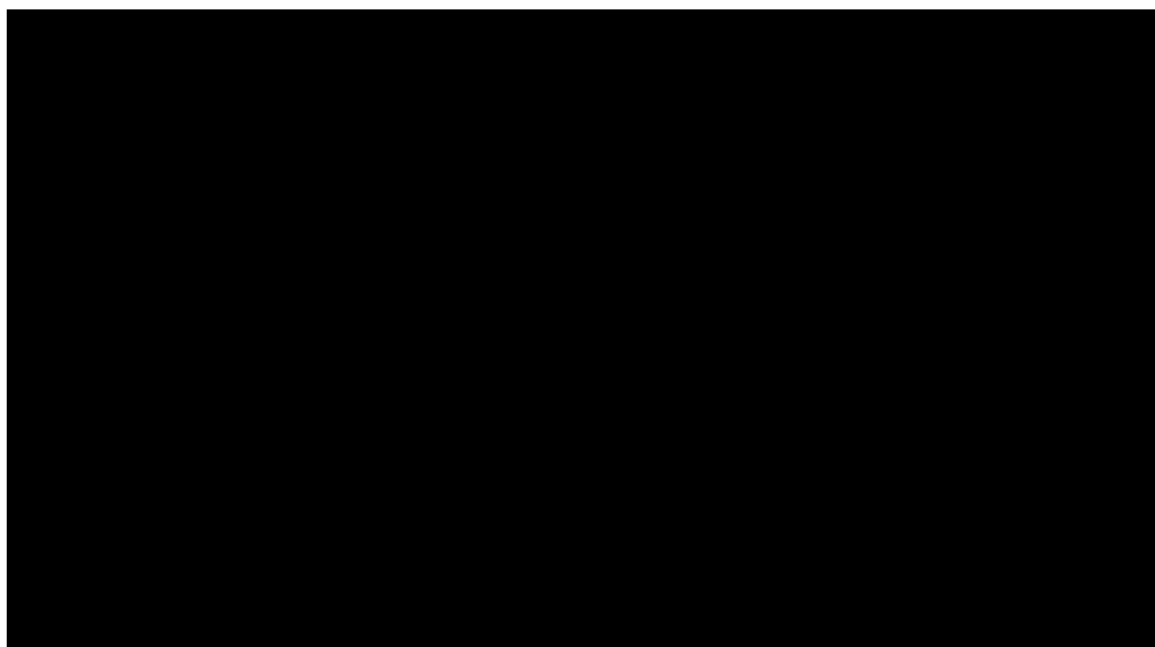


Figure 10. Tornado plot of DSA results (ICER) for epcoritamab in patients with 4L+ R/R follicular lymphoma

The company presented a range of scenario analysis including the sensitivity of cost-effectiveness estimates to alternative parametric distributions, alternative health state utility sources, alternative maximal treatment duration (i.e., 2 years vs. 3 years), alternative model time horizon, alternative resource use estimates and varying the proportion of patients who receive treatments included in the current 4L+ basket of care.

In all the company's sensitivity analyses, the company concluded that the ICER [REDACTED] the £30,000 WTP threshold. During clarification, the EAG questioned whether the company had explored any scenario whereby the basket of treatments used in current 4L+ care were costed using the actual proportions reported in the HMRN dataset. The company responded that this would have introduced complexity as 19 drug regimens would need to be included in the costs analysis (Clarification response B5). The EAG appreciates the complexity but considers that a scenario that considers the costs of the 3 most frequently used options, rather than selecting only one (particularly for chemotherapy) might better reflect treatment costs in the basket of care, whilst alleviating the complexity of costing every treatment regimen

The company also provided 2 additional scenario analyses during clarification to show the impact on ICER of: (i) including prophylactic corticosteroids, antihistamines and antipyretics that were given to patients in the expansion cohort iNHL FL 1-3A and, (ii) assuming vial sharing is not allowed in both epcoritamab and current 4L+ care arm (the base case analysis only allowed vial sharing in the epcoritamab arm). The results of these scenario analyses were consistent with the rest and suggested that, under the company's base case assumptions, the ICER for epcoritamab falls █████ 20-30,000/QALY

Table 50. Summary of scenario analyses results for epcoritamab vs. current 4L+ care: deterministic

Scenario analysis	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER/QALY (£)	Source
Base case	████	7.018	3.994	████	Table 81 (CS)
Time horizon: 10 years	████	3.955	2.800	████	Table 84 CS
Time horizon: 20 years	████	6.270	████	████	Table 84 CS
Maximal treatment duration for complete responders (2 years)	████	7.018	3.994	████	Table 85 (CS)
Alternative utility value : Utilities for PF from EPCORE NHL-1 trial (adjusted for PD using Wild et al. 2006	████	7.018	4.127	████	Table 87 (CS
Alternative utility value: Utilities for PF from EPCORE NHL-1 trial (adjusted PD from TA892)	████	7.018	4.456	████	Table 87 (CS
Alternative utility value: Wild et al. 2006	████	7.018	4.155	████	Table 87 (CS
Alternative utility value: Cognet et al. 2015	████	7.018	3.578	████	Table 87 (CS
Alternative utility value: TA892	████	7.018	4.478	████	Table 87 (CS

Scenario analysis	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER/QALY (£)	Source
Composition of current 4L+ care basket (based on TA894)	██████	7.018	3.994	██████	Table 89 (CS)
OS survival extrapolations for epcoritamab					
Log-normal	*****	7.018	3.994	*****	Table 90 (CS)
Log-logistic	██████	6.369	3.757	██████	Table 90 (CS)
Gompertz	██████	6.092	3.643	██████	Table 90 (CS)
PFS extrapolations for epcoritamab					
Log-normal	*****	7.018	3.994	*****	Table 91 (CS)
Gen. gamma	██████	7.018	4.329	██████	Table 91 (CS)
Log-logistic	██████	7.018	3.998	██████	Table 91 (CS)
Weibull	██████	7.018	3.859	██████	Table 91 (CS)
Gamma	██████	7.018	3.787	██████	Table 91 (CS)
Alternative extrapolations for TTD for epcoritamab					
Lognormal	*****	7.018	3.994	*****	Table 92 (CS)
Generalised Gamma	██████	7.018	3.994	██████	Table 92 (CS)
Log-logistic	██████	7.018	3.994	██████	Table 92 (CS)
Gompertz	██████	7.018	3.994	██████	Table 92 (CS)
Weibull	██████	7.018	3.994	██████	Table 92 (CS)
Gamma	██████	7.018	3.994	██████	Table 92 (CS)
Exponential	██████	7.018	3.994	██████	Table 92 (CS)
Applying a PFS/TTD HR (██████) to derive TTD outcomes for current 4L+ care	██████	7.018	3.994	██████	Table 93 (CS)
Using resource use estimates for haematologist visit, diagnostic scans and CT scans from TA894	██████	7.018	3.994	██████	Table 95 (CS)
Including concomitant medications	██████	7.018	3.994	██████	Table 13 (Clarification Response)

Scenario analysis	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER/QALY (£)	Source
No vial sharing for epcoritamab or current 4L+ care	██████	7.018	3.994	██████	Table 14 (Clarification Responses)

5.3 *Model validation and face validity check*

The EAG conducted an extensive review of the model submitted by the company. The model appears to reflect the assumptions made by the company and contained clinical aspects necessary to address the decision problem. The EAG sought clinical validation of (i) the model assumptions (both EAG and company's) and (ii) model's output ((LYG, QALYs) and relevant economic outcomes (e.g., treatment costs)).

6 EXTERNAL ASSESSMENT GROUP'S ADDITIONAL ANALYSES

6.1 *Exploratory and sensitivity analyses undertaken by the EAG*

Following our critique of the company's economic model, the EAG made changes to the company's model to explore the impact of individual changes to the base case results. The suggested changes along with the EAG justifications are presented below

- Using a naïve analysis to inform relative efficacy of epcoritamab vs. current 4L+ care

In section 3.4.5, the EAG provides a detailed critique of the company's MAIC and concludes that the MAIC is unhelpful and potentially mis-leading for decision-making purposes. The EAG believes that, whilst clearly flawed, a naïve comparison is probably the best approach to inform relative efficacy of epcoritamab in this case. The EAG has conducted an analysis to explore the impact on outcomes (LYG, QALYs) and costs of using a naïve analysis rather than MAIC to inform relative efficacy of epcoritamab (Table 52; Table 53). The analysis also uses Covid-

unadjusted data contrary to the company's approach where covid-adjusted data for epcoritamab was used in company's base case.

- Epcoritamab OS extrapolation

In section 3.2.5.1.1, the EAG highlighted that their clinical experts considered the company's choice of lognormal model of OS for epcoritamab to be optimistic. If maintaining the COVID-modified data used by the company in their base case, the EAG explored the use of exponential extrapolation with the lowest goodness of fit statistics and most pessimistic extrapolation of models fitted to the data to evaluate the impact of using a model with fewer parameters and less prone to overfitting in view of the small sample size and number of events.

- Using MAIC hazard ratios to the parametric extrapolation of the HMRN data to estimate the efficacy of epcoritamab.

As outlined in section 4.2.6.1, the EAG explored using the MAIC hazard ratios on the parametric extrapolation of the HMRN data to evaluate the effect of this approach on the efficacy of epcoritamab.

- Using COVID unmodified data of epcoritamab from EPCORE NHL-1

As discussed in section 4.2.6.1, the company used COVID modified data to estimate the relative efficacy of epcoritamab but the EAG prefers the use of COVID unmodified data. A scenario analysis to assess the impact of using COVID unmodified data on the cost-effectiveness results was performed.

- Using HMRN data to directly extrapolate the OS and PFS for the current 4L+ care.

It was highlighted in section 4.2.6.2 that the EAG prefers to directly extrapolate the HMRN dataset due to the concerns with the MAIC. The EAG's preferred extrapolation is a log-normal model for both PFS and OS, which had the lowest

goodness-of-fit statistics and good visual fit. A scenario analysis was performed to assess the impact of this assumption.

- Exploring alternative resource usage in the epcoritamab arm for haematologist consultant visits

In Section 4.2.8.4, it was outlined that the clinical experts to the EAG indicated that haematologist consultant visits appear to be underestimated in the epcoritamab arm. They specified that haematologist consultant visits will be weekly in first month and then monthly thereafter because patients on epcoritamab usually have weekly infusions in the first month. The EAG has explored what impact this additional resource use will have on the cost-effectiveness results (Table 54).

- Evaluate the impact of using proportions of AEs that represent AE for the therapies in the current 4L+ care basket.

As discussed in section 3.2.6.4, the company used AE for R-CHOP to represent AE of the basket of care. The EAG evaluated the impact of using varying proportion of AEs that represent all the therapies in the basket. (Table 51)

Table 51: Weighted Adverse event proportions for current 4L+ care

Adverse event	O-benda ████	R-CHOP ████	R ² ████	Weighted AE Current 4L+ care basket (%)
Neutropenia	27.50%	90.30%	42.30%	65.42%
Anaemia	5.40%	4.5%	3.10%	4.64%
Leukopenia	0.00%	30.80%	7.00%	18.58%
Lymphopenia	0.00%	0.00%	3.10%	0.33%
Thrombocytopenia	10.30%	0.00%	5.50%	3.83%
Source	CS clarification response, Table 15	CS original submission, Table 58	CS, clarification response, Table 15	

Each adverse event proportion for a sub-basket was estimated by considering the proportion of patients taking the therapy that represent each sub-basket after re-weighting the sub-basket proportions to sum up to 100%.

New weights estimated are O-Benda – ■■■■, R-CHOP – ■■■■, and R² – ■■■■

AE rate = proportion of patients taking the therapy x AE rate of the therapy..... (1)

Weighted AE rate for the current 4L+ = Sum of AE rate of the therapies estimated from (1) (2).

Only AEs that occurred in ≥ 5% of patients were included in the model.

- Estimating the impact of including grade 2 CRS that occurred in greater than 5% of patients in the EPCORE NHL-1 trial.

As discussed in section 4.2.7.4 and section 3.2.7, the company model only incorporated grade 3 or 5 TEAEs that occurred in ≥ 5% of patients. CRS which is a major TEAE related to the use of epcoritamab was excluded in the model because it did not meet this criterion. The EAG indicated that grade 2 CRS required treatment with tocilizumab. The EAG's experts noted that tocilizumab initial treatment costs are high. An exploratory analysis assessing the impact of the inclusion of all grades 2 CRS that required treatment in the optimization phase of the trial (data for expansion phase 4L+ not available) has been performed to assess the impact of company's base case assumption. This approach has been taken in previous appraisals (see section 4.2.7.4)

- Using same PFS utility for both epcoritamab arm and current 4L+ care and adjusting for PD utility with the utility decrement from wild et al, 2006.

It was discussed in section 4.2.7.3 that utilities obtained by adjusting for CR status may be biased in favour of epcoritamab and that the EAG prefers to use the same PFS and PD utilities for both arms. A scenario analysis was performed to assess this assumption.

- Applying AE disutility in the base case analysis.

In section 4.2.7.3 , it was highlighted that AE disutilities were excluded from the company's base case analysis. The EAG have included AE disutility to evaluate its impact on the cost-effectiveness results (Table 54).

The EAG also corrected an error in the application of LDH cost in the company's model (section 4.2.8.4).

6.2 Impact on the ICER of additional clinical and economic analyses undertaken by the EAG

Table 52, Table 53 and Table 54 show the EAG's main exploratory analyses and the impact on outcomes (LYG, QALYs, costs, ICER).

In Table 52, the mean LYG in progression-free vs progressed disease state are shown for the EAG's exploratory naïve analysis. The company's results, based on the MAIC analysis are also shown for comparison.

Table 52: Mean LYG for epcoritamab vs current 4L+care - EAG naïve comparison vs. company's MAIC- adjusted base case analysis

Analytical approach	EAG's naïve comparison		Company's MAIC analysis	
	Epcoritamab	Current 4L+ care	Epcoritamab	Current 4L+ care
Mean life years				
Progression free				
Progressed				
Time on treatment*				

Table 53: Deterministic cost-effectiveness results - EAG naïve comparison

Technology		Total discounted costs	Total discounted QALYs	Mean LYG	ICER of Epco vs Comparator
Epcoritamab			3.599	5.664	-
Current 4L+ Care			1.890	2.804	-
Difference			1.709	2.860	

Table 53 above shows the cost-effectiveness results for epcoritamab vs current 4L+ care when a naïve comparison and Covid-unadjusted data are used. The ICER increases to [REDACTED] from [REDACTED] (company's base case), representing a 110% increase in ICER.

Table 54 summarises the rest of the EAG's deterministic cost-effectiveness results for the exploratory analyses.

Table 54: EAG exploratory analyses - epcoritamab vs current 4L+ care

Parameter varied	Base case value	Scenario value	Rationale	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Change in ICER
Company base case					■	3.994	■	
Epcoritamab OS extrapolation	Lognormal	Exponential	The most pessimistic as it has the lowest goodness-of-fit statistics and produced the most pessimistic extrapolation of the models fitted to the data	Epcoritamab : 4.130 Current 4L+: 1.106	■	3.023	■	■)
MAIC hazard ratios	MAIC hazard ratios on unadjusted epcoritamab extrapolations	MAIC hazard ratios on extrapolations of HMRN data	To evaluate the impact of a different approach in assessing the efficacy of epcoritamab	Epcoritamab : 6.336 Current 4L+: 1.890	■	4.445	■	■)

Parameter varied	Base case value	Scenario value	Rationale	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Change in ICER
Company base case						3.994		
Log-normal extrapolations for PFS and OS for epcoritamab.	Log-normal extrapolations for PFS and OS for epcoritamab based on Covid adjusted data from EPCORE NHL -1	Log-normal extrapolations for PFS and OS for epcoritamab based on COVID unadjusted data from EPCORE NHL -1	To assess the impact of using COVID unmodified epcoritamab data on cost-effectiveness results.	Epcoritamab : 3.599 Current 4L+: 0.737		2.862		
Survival extrapolations for current 4L+ care	MAIC HR used on adjusted epcoritamab data from EPCORE NHL-1 to get PFS and OS extrapolations for current 4L+ care.	Log-normal extrapolations for both PFS and OS for current 4L+ care using HMRN data directly	To evaluate the impact of using a different approach to get the survival outcomes for the current 4L+ care.	Epcoritamab : 5.176 Current 4L+: 1.890		3.286		

Parameter varied	Base case value	Scenario value	Rationale	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Change in ICER
Company base case					██████	3.994	██████	
Resource use (Haematologist consultant visit)	Once a month	Once weekly (cycle 0-4), then once monthly	To evaluate the impact of haematologist consultation visits based on EAG clinical expert advice.	Epcoritamab : 5.176 Current 4L+: 1.182	██████	3.994	██████	██████)
Resource use (PET scans)	Not included	Once in a year	To explore the impact of the addition of PET scans to the resource use in PFS based on EAG clinical expert advice.	Epcoritamab : 5.176 Current 4L+: 1.182	██████	3.994	██████	██████)
Adverse Events proportions in the current 4L+	AEs recorded for R-CHOP in TA892	Weighted proportions based on AEs for O-benda, R-CHOP and R ²	To Evaluate the AEs in the current 4L+ based on AEs that represent the varying proportions of AEs across the therapies in the basket of care.	Epcoritamab : 5.176 Current 4L+: 1.182	██████	3.994	██████	██████████
Grade 2 CRS AE occurring in > 5%	CRS = 0.00%	CRS = 12%	To assess the impact of	Epcoritamab : 5.176	██████	3.994	██████	██████████

Parameter varied	Base case value	Scenario value	Rationale	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Change in ICER
Company base case					████	3.994	████	
in epcoritamab arm.			including CRS AE in the epcoritamab arm	Current 4L+: 1.182				
Utility for PFS and PD state.	Epcoritamab PFS: █████ Current 4L+ PFS: █████ PD: █████	PFS utility arms =0.800 PD =0.613	To explore the impact of using the same health state utility for both arms.	Epcoritamab : 5.414 Current 4L+: 1.287	████	4.127	████	████
AE disutility	No AE disutility included	AE disutility included	To assess the AE disutility on QALYs	Epcoritamab : 5.169 1.176	████	3.993	████	████

*Change in ICER based on company's base case as presented in CS. However, table 55 presents the updated base case (corrected for LDH cost).

6.3 EAG's preferred assumptions

Based on all considerations in Section 3.4 and 4.2 of this report, the EAG defined a new base case. The adjustments made to the company model are described below and impact on QALYs and incremental costs summarised in Table 55. All deterministic ICERs for the individual changes reported in Table 55 apply a severity modifier. However, the cumulative impact of all changes (i.e., EAG's base case) does not include a severity modifier as EAG's QALY shortfall calculations based on EAG's preferred assumptions indicates that a severity modifier does not apply for this appraisal (section 4.2.9). The last row in Table 55 presents results with severity modifier as sensitivity analysis to maintain consistency with company's approach and allow comparison with company's severity-adjusted results.

Table 55. EAG preferred assumptions

Preferred assumption	Section in EAG report	Total QALYs	Incremental Costs	Incremental QALYs	ICER £/QALY	Change in ICER
Company's base case		Epcoritamab: 5.176 Current 4L+: 1.182	■	3.994	■	
*Correction for LDH cost application for PFS state ^a	4.2.8.4	Epcoritamab: 5.176 Current 4L+: 1.182	■	3.994	■	
<i>Survival modelling approach for epcoritamab and current 4L+ care</i>						
Epcoritamab:						

Preferred assumption	Section in EAG report	Total QALYs	Incremental Costs	Incremental QALYs	ICER £/QALY	Change in ICER
EAG 01: Log-normal extrapolations for PFS and OS for epcoritamab based on <i>Covid unadjusted data</i> from EPCORE NHL -1 ^b	4.2.6.1	Epcoritamab: 3.599 Current 4L+: 0.737		2.862		
Current 4L+ Care						
EAG 02: Log-normal extrapolations for both PFS and OS for current 4L+ care using HMRN data directly ^c	4.2.6.1	Epcoritamab: 5.176 Current 4L+: 1.890		3.286		
Cumulative impact of EAG 01 – EAG 02 (naïve analysis)	4.2.6.1.1 6.1	Epcoritamab: 3.599 Current 4L+: 1.890		1.709		
<i>Alternative resource usage</i>						

Preferred assumption	Section in EAG report	Total QALYs	Incremental Costs	Incremental QALYs	ICER £/QALY	Change in ICER
EAG 03: Higher frequency of haematologist consultant visits in the first month in epcoritamab arm	4.2.8.4	Epcoritamab: 5.176 Current 4L+: 1.182	████████	3.994	████████	████████ ↓
<i>Utilities for PFS and PD</i>						
EAG 04: Utilities for PFS from EPCORE NHL-1 trial, adjusted for PD using wild et al		Epcoritamab: 5.414 Current 4L+: 1.287	████████	4.127	████████	████████
<i>Adverse events</i>						
EAG 05: Adverse events incidence in comparator arm based on reweighted data for R-CHOP (RELEVANCE), O-Benda (GADOLIN) and R ² (MAGNIFY) as reported in TA894 ^d	4.2.7.4	Epcoritamab: 5.176 Current 4L+: 1.182	████████	3.994	████████	████████

Preferred assumption	Section in EAG report	Total QALYs	Incremental Costs	Incremental QALYs	ICER £/QALY	Change in ICER
EAG 06: Inclusion of grade 2 CRS events requiring treatment with tocilizumab	4.2.7.4 4.2.8.5	Epcoritamab: 5.176 Current 4L+: 1.182		3.994		
Cumulative impact of all changes (EAG01 – EAG06)^e		Epcoritamab: 3.131 Current 4L+: 1.705		1.427		
Sensitivity Analysis: Cumulative impact of all changes (EAG01 – EAG06)^f		Epcoritamab: 3.131 Current 4L+: 1.705		1.71		
^aChange in ICER based on company's corrected base case ICER of  ^b Company's base case analysis uses covid-modified data but choice of extrapolations (log-normal) is the same as in EAG's base case ^c Company applies HRs obtained from their preferred MAIC to the PFS and OS extrapolations of epcoritamab ^d Company uses data for R-CHOP only ^e.EAG base case does not apply severity modifier ^f Sensitivity analysis: x1.2 severity modifier applied to incremental QALYs. This is similar to comparing the EAG's base ICER with company's (corrected) severity unadjusted ICER of 						

6.3.1 EAG Deterministic base case results

The cumulative effect of all EAG changes on deterministic cost-effectiveness results is shown in Table 56.

Table 56. Deterministic EAG base cost-effectiveness results with epcoritamab PAS discount

	Total Costs (£)	Total LYG	Total QALYs	Incremental Costs of Epcoritamab (£)	Incremental LYG of Epcoritamab	Incremental QALYs of Epcoritamab	ICER (£/QALYs)
Epcoritamab	████████	5.664	3.131				
Current 4L+Care	████████	2.804	1.705	████████	2.860	1.427	████████

*Analysis does not include severity modifier

Deterministic incremental costs were ██████████ and incremental QALYs were 1.427 which resulted in an ICER of £████████/QALY which was ██████████ than the company's base case severity unadjusted ICER (corrected for LDH cost) of £████████. A summary of net health benefits, at £30,000 threshold is shown in Table 57 below.

Table 57: Net benefit results in the EAG's base case analysis

Net monetary benefit (NMB) at £30,000	Net health benefit (NHB) at £30,000
████████	████████

6.3.2 EAG's probabilistic base case cost-effectiveness results

The EAG's base case was subjected to a probabilistic sensitivity analysis using 1,000 iterations drawn from the EAG parametric assumptions. The probabilistic incremental costs were ██████████ and incremental QALYs were 1.453 resulting in an ICER of ██████████ (Table 58)

Table 58. Probabilistic cost-effectiveness results, EAG base case with epcoritamab PAS discount

	Mean Total Costs (£)	Mean Total QALYs	Incremental Costs of Epcoritamab (£)	Incremental QALYs of Epcoritamab	ICER (£/QALYs)
Epcoritamab	████████	3.197			
Current 4L+Care	████████	1.744	████████	1.453	████████

The probability of epcoritamab being cost-effective at £30,000 threshold is ■. The EAG's cost-effectiveness scatterplots is presented in Figure 11 and cost-effectiveness acceptability curve in Figure 12.

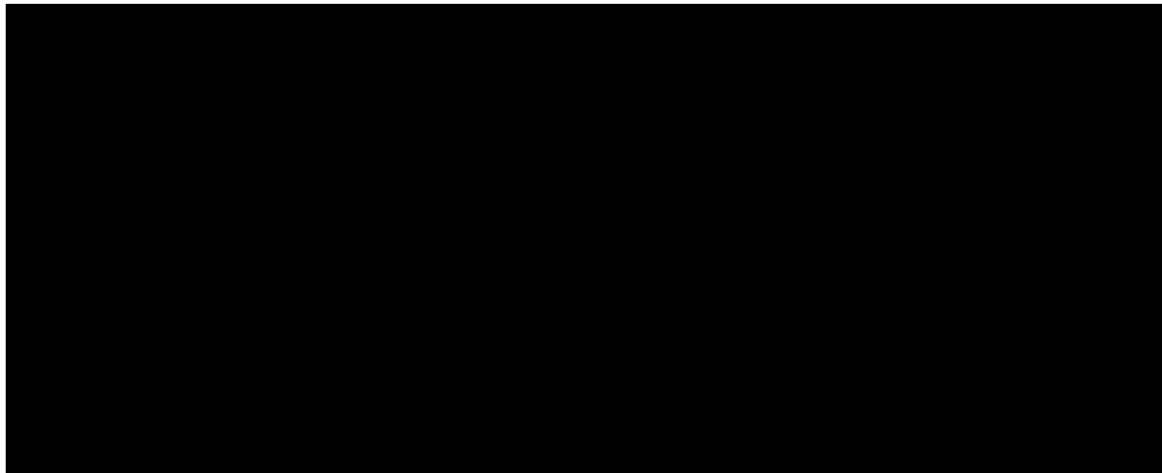


Figure 11. Incremental cost-effectiveness scatterplot of epcoritamab versus current 4L+ care, EAG base case

*Analysis does not include severity modifier; a PAS discount is applied for epcoritamab

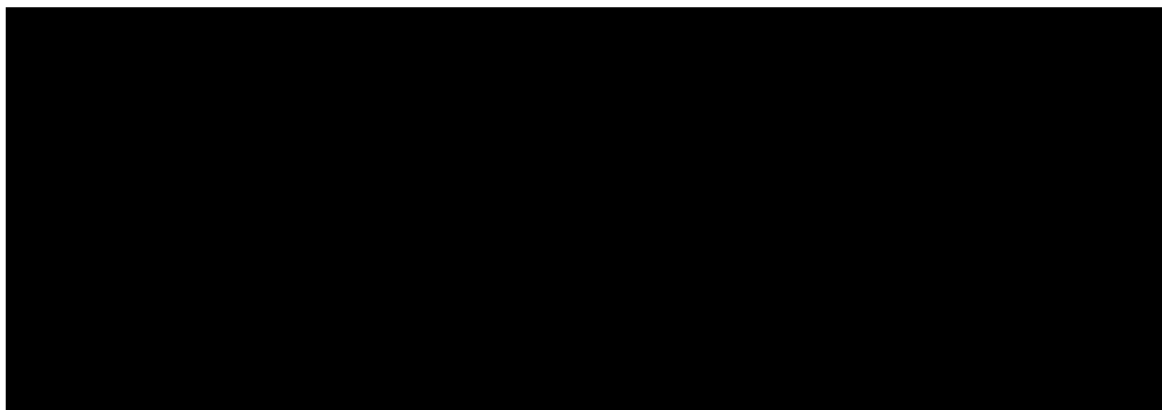


Figure 12. Cost-effectiveness acceptability curve of epcoritamab versus current 4L+ care

6.4 *Conclusions of the cost-effectiveness section*

In summary, the model constructed by the company appears to be logical and company's systematic literature searches comprehensive.

The EAG has the following concerns regarding the cost-utility analysis (as detailed in Section 1.1):

- Uncertainty in the estimates of relative effectiveness of epcoritamab compared with current 4L+ care obtained from the MAIC. The EAG notes the following concerns related to the MAIC:
 - potential for relative efficacy estimates being biased by outcomes of a small number of individuals due to small sample sizes of the MAIC weighted population (n=40) and HMRN cohort (■■■■).
 - stricter inclusion/exclusion criteria of the EPCORE NHL-1 study means methodology of MAIC is unlikely to account for the differences between a trial and real-world population
 - Counterintuitively, the MAIC adjustment resulted in hazard ratios that favoured ■■■■■ than in the unadjusted analysis, when one would expect the effect size to attenuate after adjusting, not improve. This further calls into question the face validity of the MAIC results.
- Choice of data source to inform efficacy estimates for epcoritamab which results in widely varying estimates of QALY gains.
 - Using covid-adjusted data for Epcoritamab appears inconsistent with approach used for HRMN data which does not appear to be adjusted for COVID-19 deaths.
- Choice and source of data for modelling efficacy of comparator treatment which results in widely varying estimates of QALY gains
 - The EAG generally agrees with the company that the HMRN dataset is probably the best currently available data on current 4L+ care in the UK. However, it is RWE data, that is missing key prognostic variables and where patient recruitment does not follow a strict inclusion/exclusion criterion. A larger real-world comparator cohort with

more complete data on key prognostic variables could improve the validity of an adjusted comparison.

- Other important factors that had an impact on the cost-effectiveness results (either costs or QALYs) included:
 - Health state utility values applied in the model which differed between the treatment arms and were adjusted for complete response status. The EAG preferred to apply the same utility values to both treatment arms using data derived directly from the EPCORE NHL-1 study without adjustment for CR status
 - Source of incidence data for adverse events for the comparator treatment which the EAG preferred to be weighted based on 3 out of the 4 treatments included in the sub-basket of care for current 4L+care and not based on data for R-CHOP only.

The EAG could not explore any uncertainty in relative cost-effectiveness if the population under consideration fully matched that described in NICE's final scope and UK marketing authorisation, ie., 3L+.

The EAG have presented scenarios with a preferred base-case analysis. The ICER has [REDACTED] compared with the CS, except for PFS utilities where the ICER has [REDACTED]. The EAG's preferred naïve unadjusted comparison results in a [REDACTED] in the ICER. The EAG acknowledges the limitations of an unadjusted analysis but maintains that for the reasons stated above, this approach may better represent relative efficacy. Nonetheless, the EAG's results of the cost-utility analysis should also be interpreted with caution.

- Overall, in the absence of a head-to-head comparative study that evaluates efficacy of epcoritamab compared to current care, the relative efficacy of epcoritamab remains an area of great uncertainty.

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8 Appendices

8.1.1 Additional EAG searches

CLINICAL EFFECTIVENESS – updating company’s November 2024 search

Ovid Embase, date searched: 13/05/25

Embase <1974 to 2025 May 12>

<https://ovidsp.ovid.com/ovidweb.cgi?T=JS&NEWS=N&PAGE=main&SHAREDSEARCHID=4jIHLExW0abm8UwHKg6E20D9oIV0v5IIQWwyvKvLohIXJPjJjNaKYe1f1vNIvsMKk>

- 1 exp follicular lymphoma/ 23336
- 2 (((follicul* or nodular* or histiocytic*) adj3 lymphom*) or "brill symmers" or FL).ab,ti. 64700
- 3 non-Hodgkin lymphoma/ 72536
- 4 (indolent or low grade or slow growing or non aggressive).ab,ti. 147473
- 5 1 or 2 72323
- 6 3 and 4 5624
- 7 5 or 6 76260
- 8 ((second or third or fourth or later) adj4 line).ab,ti. 75582
- 9 (refractory or intoleran* or failure* or resistan* or recurren* or metasta* or progress* or invasive* or chemorefractory or advanced or relapse*).ab,ti. 7915318
- 10 ((previous* or prior or salvage) adj4 (treat* or therap* or regimen*)).ab,ti. 329711
- 11 8 or 9 or 10 8075297
- 12 7 and 11 28677
- 13 rituximab/ or epcoritamab/ or obinutuzumab/ or lenalidomide/ or bendamustine/ 154567
- 14 (epcoritamab or epkinly* or "gen 3013" or gen3013 or tepkinly*).ab,kf,ti,tn. 272
- 15 (obinutuzumab or afutuzumab or "ga 101" or ga101 or gazyva* or "r 7159" or r7159 or "rg 7159" or rg7159 or "ro 5072759" or ro5072759).ab,kf,ti,tn. 3231
- 16 (lenalidomide or "cc 5013" or cc5013 or "cdc 501" or "cdc 5013" or cdc501 or cdc5013 or revlimid* or zelvina*).ab,kf,ti,tn. 19693
- 17 (bendamustine or levact* or belrapzo* or bendeka* or treanda* or vivimusta*).ab,kf,ti,tn. 6339
- 18 (rituximab or mabthera* or Rituxan* or Truxima* or Ruxience* or Riabri* or R-CHOP).ab,kf,ti,tn. 77907
- 19 13 or 14 or 15 or 16 or 17 or 18 162647
- 20 12 and 19 8092
- 21 (case adj2 (stud* or report)).ab,ti. 1172379
- 22 case study/ or abstract report/ or letter/ 1483994
- 23 conference proceeding.su. 4281
- 24 (conference abstract or editorial or letter or note).pt. 8672624
- 25 21 or 22 or 23 or 24 9733799
- 26 20 not 25 3822
- 27 limit 26 to dc=20241107-20250513 261
- 28 limit 26 to dd=20241107-20250513 249

ProQuest MEDLINE, date searched 13/05/25

Set#	Searched for	Databases	Results
S1	MESH.EXACT.EXPLODE("Lymphoma, Follicular")	MEDLINE®	7328
S3	TI,AB(((follicul* OR nodular* OR histiocytic*) NEAR/2 lymphom*) OR "brill symmers" OR FL)	MEDLINE®	36528
S4	MESH.EXACT("Lymphoma, Non-Hodgkin")	MEDLINE®	36848
S5	TI,AB(indolent OR "low grade" OR "slow growing" OR "non aggressive")	MEDLINE®	95085
S6	[S1] OR [S3]	MEDLINE® These databases are searched for part of your query.	38362
S7	[S4] AND [S5]	MEDLINE® These databases are searched for part of your query.	2856
S8	[S6] OR [S7]	MEDLINE® These databases are searched for part of your query.	40691
S9	TI,AB((second OR third OR fourth OR later) NEAR/3 line)	MEDLINE®	46119
S10	TI,AB(refractory or intoleran* or failure* or resistan* or recurren* or metasta* or progress* or invasive* or chemorefractory or advanced or relapse*)	MEDLINE®	5680702
S11	TI,AB((previous* or prior or salvage) NEAR/3 (treat* or therap* or regimen*))	MEDLINE®	172715
S12	[S9] OR [S10] OR [S11]	MEDLINE® These databases are searched for part of your query.	5784315
S13	[S8] AND [S12]	MEDLINE® These databases are searched for part of your query.	11429
S14	noft(epcoritamab or epkinly* or "gen 3013" or gen3013 or tepkinly*) OR noft(obinutuzumab	MEDLINE®	42772

	or afutuzumab or "ga 101" or ga101 or gazyva* or "r 7159" or r7159 or "rg 7159" or rg7159 or "ro 5072759" or ro5072759) OR noft(lenalidomide or "cc 5013" or cc5013 or "cdc 501" or "cdc 5013" or cdc501 or cdc5013 or revlimid* or zelvina*) OR noft(bendamustine or levact* or belrapzo* or bendeka* or treanda* or vivimusta*) OR noft(rituximab or mabthera* or Rituxan* or Truxima* or Ruxience* or Riabri* or "R-CHOP")		
S15	[S13] AND [S14]	MEDLINE® These databases are searched for part of your query.	1974
S16	TI,AB(case NEAR/1 (stud* OR report))	MEDLINE®	1039798
S17	RTYPE("Case reports")	MEDLINE®	2478370
S18	RTYPE("Letter")	MEDLINE®	1294496
S19	RTYPE("Historical article")	MEDLINE®	374085
S20	RTYPE("Editorial")	MEDLINE®	726453
S21	[S16] OR [S17] OR [S18] OR [S19] OR [S20]	MEDLINE® These databases are searched for part of your query.	5059003
S22	[S15] NOT [S21]	MEDLINE® These databases are searched for part of your query.	1680
S24	DCRE(>20241107)	MEDLINE®	830945
S25	[S22] AND [S24]	MEDLINE® These databases are searched for part of your query.	48

CLINICAL EFFECTIVENESS – additional checks for missed studies

Embase (Ovid) searched 20/05/25

Embase <1974 to 2025 May 19>

- 1 exp follicular lymphoma/ 23603
- 2 ((follicul* or nodular* or histiocytic*) adj3 lymphom*).ab,ti,kf. 22157
- 3 non-Hodgkin lymphoma/ 73003
- 4 (indolent or low grade or slow growing or non aggressive).ab,ti,kf. 149077
- 5 1 or 2 29450

6 3 and 4 5721
 7 5 or 6 33506
 8 ((second or third or fourth or later) adj4 line).ab,ti,kf. 76721
 9 (refractory or intoleran* or failure* or resistan* or recurren* or metasta* or progress* or
 invasive* or chemorefractory or advanced or relapse*).ab,ti,kf. 8044480
 10 ((previous* or prior or salvage) adj4 (treat* or therap* or regimen*)).ab,ti,kf. 333774
 11 refractory cancer/ or cancer recurrence/ or salvage therapy/ 331503
 12 8 or 9 or 10 or 11 8244837
 13 7 and 12 17703
 14 rituximab/ or epcoritamab/ or obinutuzumab/ or lenalidomide/ or bendamustine/
 155386
 15 (epcoritamab or epkinly* or "gen 3013" or gen3013 or tepkinly*).ab,kf,ti,tn. 275
 16 (obinutuzumab or afutuzumab or "ga 101" or ga101 or gazyva* or "r 7159" or r7159 or "rg
 7159" or rg7159 or "ro 5072759" or ro5072759).ab,kf,ti,tn. 3286
 17 (lenalidomide or "cc 5013" or cc5013 or "cdc 501" or "cdc 5013" or cdc501 or cdc5013
 or revlimid* or zelvina*).ab,kf,ti,tn. 19922
 18 (bendamustine or levact* or belrapzo* or bendeka* or treanda* or vivimusta*).ab,kf,ti,tn.
 6414
 19 (rituximab or mabthera* or Rituxan* or Truxima* or Ruxience* or Riabri* or R-
 CHOP).ab,kf,ti,tn. 78415
 20 14 or 15 or 16 or 17 or 18 or 19 163493
 21 13 and 20 8179
 22 (case adj2 (stud* or report)).ab,ti,kf. 1185979
 23 case study/ or abstract report/ or letter/ 1485130
 24 conference proceeding.su. 4281
 25 (conference abstract or editorial or letter or note).pt. 8679861
 26 (exp animal/ or exp animal experiment/) not (exp human/ or exp human experiment/)
 5961998
 27 22 or 23 or 24 or 25 or 26 15089833
 28 21 not 27 4129
 29 limit 28 to dc=20230403-20250520 648
 30 limit 28 to dd=20230403-20250520 621
 31 29 or 30 649
 32 limit 31 to yr="2022 - 2025" 401
 33 "clinicaltrials.gov".jn. 179697
 34 32 not 33 393

MEDLINE (Ovid) searched 20/05/25
 Ovid MEDLINE(R) ALL <1946 to May 19, 2025>

1 exp Lymphoma, Follicular/ 7345
 2 (((follicul* or nodular* or histiocytic*) adj3 lymphom*) or brill symmers or FL).tw,kf.
 36555
 3 Lymphoma, Non-Hodgkin/ 36868
 4 (indolent or low grade or slow growing or non aggressive).tw,kf. 96306
 5 1 or 2 38213
 6 3 and 4 2859

7 5 or 6 40508
 8 ((second or third or fourth or later) adj4 line).tw,kf. 41489
 9 (refractory or intoleran* or failure* or resistan* or recurren* or metasta* or progress* or
 invasive* or chemorefractory or advanced or relapse*).ab,ti,kf. 5784908
 10 ((previous* or prior or salvage) adj4 (treat* or therap* or regimen*)).ab,ti,kf. 168563
 11 Recurrence/ 206806
 12 8 or 9 or 10 or 11 5942445
 13 7 and 12 11643
 14 Rituximab/ or Antibodies, Bispecific/ or Lenalidomide/ or Bendamustine Hydrochloride/
 29545
 15 (epcoritamab or epkinly* or "gen 3013" or gen3013 or tepkinly*).ab,kf,ti,nm. 94
 16 (obinutuzumab or afutuzumab or "ga 101" or ga101 or gazyva* or "r 7159" or r7159 or "rg
 7159" or rg7159 or "ro 5072759" or ro5072759).ab,kf,ti,nm. 1162
 17 (lenalidomide or "cc 5013" or cc5013 or "cdc 501" or "cdc 5013" or cdc501 or cdc5013
 or revlimid* or zelvina*).ab,kf,ti,nm. 6847
 18 (bendamustine or levact* or belrapzo* or bendeka* or treanda* or
 vivimusta*).ab,kf,ti,nm. 2100
 19 (rituximab or mabthera* or Rituxan* or Truxima* or Ruxience* or Riabri* or R-
 CHOP).ab,kf,ti,nm. 35484
 20 14 or 15 or 16 or 17 or 18 or 19 47733
 21 13 and 20 2070
 22 (case reports or editorial or historical article or letter).pt. 4620643
 23 (case adj2 (stud* or report)).ab,ti,kf. 918461
 24 exp animals/ not humans.sh. 5347725
 25 22 or 23 or 24 10229890
 26 21 not 25 1762
 27 ("20230403" or "20230404" or "20230405" or "20230406" or "20230407" or "20230408"
 or "20230409" or 2023041* or 2023042* or "20230430" or 202305* or 202306* or 202307* or
 202308* or 202309* or 20231* or 2024* or 2025*).dt,ez,da,ed. 3618111
 28 26 and 27 190
 29 limit 28 to yr="2022 -Current" 190

COST EFFECTIVENESS & COSTS

MEDLINE for economic evaluations and costs - searched 15/05/25

Ovid MEDLINE(R) ALL <1946 to May 14, 2025>

1 exp Lymphoma, Follicular/ 7342
 2 (((follicul* or nodular* or histiocytic*) adj3 lymphom*) or brill symmers or FL).tw.
 36080
 3 Lymphoma, Non-Hodgkin/ 36859
 4 (indolent or low grade or slow growing or non aggressive).tw. 95423
 5 1 or 2 37849
 6 3 and 4 2855
 7 5 or 6 40153
 8 ((second or third or fourth or later) adj4 line).tw. 41172

9 (refractory or intoleran* or failure* or resistan* or recurren* or metasta* or progress* or invasive* or chemorefractory or advanced or relapse*).ab,ti. 5707414

10 ((previous* or prior or salvage) adj4 (treat* or therap* or regimen*)).ab,ti. 167879

11 Recurrence/ 206630

12 8 or 9 or 10 or 11 5865384

13 7 and 12 11469

14 Economics/ 27544

15 exp "Costs and Cost Analysis"/ 279095

16 Economics, Nursing/ 4013

17 Economics, Medical/ 9305

18 Economics, Pharmaceutical/ 3162

19 exp Economics, Hospital/ 26207

20 Economics, Dental/ 1922

21 exp "Fees and Charges"/ 31686

22 exp Budgets/ 14346

23 budget*.ti,ab,kf. 40284

24 (economic* or cost or costs or costly or costing or price or prices or pricing or pharmaco-economic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ti,kf. 313355

25 (economic* or cost or costs or costly or costing or price or prices or pricing or pharmaco-economic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ab. /freq=2 440183

26 (cost* adj2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)).ab,kf. 248742

27 (value adj2 (money or monetary)).ti,ab,kf. 3429

28 exp models, economic/ 16843

29 economic model*.ab,kf. 4753

30 markov chains/ 17095

31 markov.ti,ab,kf. 32999

32 monte carlo method/ 34221

33 monte carlo.ti,ab,kf. 66890

34 exp Decision Theory/ 14364

35 (decision* adj2 (tree* or analy* or model*)).ti,ab,kf. 50109

36 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 [economic evaluations & models filter from CADTH
<https://searchfilters.cadth.ca/link/16>]1013700

37 ec.fs. or cost.tw. or health care costs.sh. [ovid Clinical Queries – Economics – Maximized Sensitivity – Ovid MEDLINE] 967108

38 Economics/ or "costs and cost analysis"/ or "Cost allocation"/ or "Cost-benefit analysis"/ or "Cost control"/ or "Cost savings"/ or "Cost of illness"/ or "Cost sharing"/ or "deductibles and coinsurance"/ or "Medical savings accounts"/ or "Health care costs"/ or "Direct service costs"/ or "Drug costs"/ or "Employer health costs"/ or "Hospital costs"/ or "Health expenditures"/ or "Capital expenditures"/ or "Value of life"/ or exp "economics, hospital"/ or exp "economics, medical"/ or "Economics, nursing"/ or "Economics, pharmaceutical"/ or exp "fees and charges"/ or exp budgets/ or (low adj cost).mp. or (high adj cost).mp. or (health?care adj cost\$).mp. or (fiscal or funding or financial or finance).tw. or (cost adj estimate\$).mp. or (cost adj variable).mp. or (unit adj cost\$).mp. or (economic\$ or

pharmacoeconomic\$ or price\$ or pricing).tw. [SIGN search filter - Economics , MEDLINE]
1057542
39 13 and 36 227
40 13 and 37 236
41 13 and 38 270
42 39 or 40 or 41 409
43 (202304* or 2024* or 2025*).dt,ez,da,ed. [added to Medline since company's initial
search in April 2023] 2581901
44 42 and 43 74

Embase - for economic evaluations and costs - searched 15/05/25

Embase <1974 to 2025 May 14>

1 exp follicular lymphoma/ 23347
2 (((follicul* or nodular* or histiocytic*) adj3 lymphom*) or "brill symmers" or FL).ab,ti.
64745
3 non-Hodgkin lymphoma/ 72545
4 (indolent or low grade or slow growing or non aggressive).ab,ti. 147541
5 1 or 2 72369
6 3 and 4 5625
7 5 or 6 76307
8 ((second or third or fourth or later) adj4 line).ab,ti. 75634
9 (refractory or intoleran* or failure* or resistan* or recurren* or metasta* or progress* or
invasive* or chemorefractory or advanced or relapse*).ab,ti. 7920803
10 ((previous* or prior or salvage) adj4 (treat* or therap* or regimen*)).ab,ti. 329883
11 refractory cancer/ or cancer recurrence/ or salvage therapy/ 331017
12 8 or 9 or 10 or 11 8121500
13 7 and 12 29226
14 Economics/ 246191
15 Cost/ 65761
16 exp Health Economics/ 1131274
17 Budget/ 36231
18 budget*.ti,ab,kw. 52406
19 (economic* or cost or costs or costly or costing or price or prices or pricing or
pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or
expenses or financial or finance or finances or financed).ti,kw. 344179
20 (economic* or cost or costs or costly or costing or price or prices or pricing or
pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or
expenses or financial or finance or finances or financed).ab. /freq=2 612353
21 (cost* adj2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or
outcomes)).ab,kw. 329849
22 (value adj2 (money or monetary)).ti,ab,kw. 4518
23 Statistical Model/ 180689
24 economic model*.ab,kw. 7025
25 Probability/ 166473
26 markov.ti,ab,kw. 41041
27 monte carlo method/ 57425
28 monte carlo.ti,ab,kw. 68486

29 Decision Theory/ 1913
 30 Decision Tree/ 28552
 31 (decision* adj2 (tree* or analy* or model*)).ti,ab,kw. 64181
 32 or/14-31 [Economic Evaluations & Models - Embase. In: CADTH Search Filters
 Database. Ottawa: CADTH; 2023: <https://searchfilters.cadth.ca/link/15.>] 2217668
 33 13 and 32 1453
 34 limit 33 to dc=20230401-20250515 307
 35 limit 33 to dd=20230401-20250515 298
 36 limit 33 to rd=20230401-20250515 139
 37 34 or 35 or 36 321

HEALTH-RELATED QUALITY OF LIFE

MEDLINE for health-related quality of life – searched 15/05/25

Ovid MEDLINE(R) ALL <1946 to May 14, 2025>

1 exp Lymphoma, Follicular/ 7342
 2 (((follicul* or nodular* or histiocytic*) adj3 lymphom*) or brill symmers or FL).tw. 36080
 3 Lymphoma, Non-Hodgkin/ 36859
 4 (indolent or low grade or slow growing or non aggressive).tw. 95423
 5 1 or 2 37849
 6 3 and 4 2855
 7 5 or 6 40153
 8 ((second or third or fourth or later) adj4 line).tw. 41172
 9 (refractory or intoleran* or failure* or resistan* or recurren* or metasta* or progress* or
 invasive* or chemorefractory or advanced or relapse*).ab,ti. 5707414
 10 ((previous* or prior or salvage) adj4 (treat* or therap* or regimen*)).ab,ti. 167879
 11 Recurrence/ 206630
 12 8 or 9 or 10 or 11 5865384
 13 7 and 12 11469
 14 "Value of Life"/ 5835
 15 Quality of Life/ 305763
 16 quality of life.ti,kf. 136906
 17 ((instrument or instruments) adj3 quality of life).ab. 4235
 18 Quality-Adjusted Life Years/ 17827
 19 quality adjusted life.ti,ab,kf. 20147
 20 (qaly* or qald* or qale* or qtime* or life year or life years).ti,ab,kf. 33896
 21 disability adjusted life.ti,ab,kf. 7799
 22 daly*.ti,ab,kf. 7045
 23 (sf36 or sf 36 or short form 36 or shortform 36 or short form36 or shortform36 or sf
 thirtysix or sfthirtysix or sfthirty six or sf thirty six or shortform thirtysix or shortform thirty six or
 short form thirtysix or short form thirty six).ti,ab,kf. 33630
 24 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form
 six or shortform6 or short form6).ti,ab,kf. 2968

25 (sf8 or sf 8 or sf eight or sflight or shortform 8 or shortform 8 or shortform8 or short form8 or shortform eight or short form eight).ti,ab,kf. 682

26 (sf12 or sf 12 or short form 12 or shortform 12 or short form12 or shortform12 or sf twelve or sftwelve or shortform twelve or short form twelve).ti,ab,kf. 8723

27 (sf16 or sf 16 or short form 16 or shortform 16 or short form16 or shortform16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).ti,ab,kf. 43

28 (sf20 or sf 20 or short form 20 or shortform 20 or short form20 or shortform20 or sf twenty or sftwenty or shortform twenty or short form twenty).ti,ab,kf. 483

29 (hql or hqol or h qol or hrqol or hr qol).ti,ab,kf. 28318

30 (hye or hyes).ti,ab,kf. 79

31 (health* adj2 year* adj2 equivalent*).ti,ab,kf. 48

32 (pqol or qls).ti,ab,kf. 512

33 (quality of wellbeing or quality of well being or index of wellbeing or index of well being or qwb).ti,ab,kf. 817

34 nottingham health profile*.ti,ab,kf. 1286

35 sickness impact profile.ti,ab,kf. 1106

36 exp health status indicators/ 360983

37 (health adj3 (utilit* or status)).ti,ab,kf. 104681

38 (utilit* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or weight)).ti,ab,kf. 18394

39 (preference* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or instrument or instruments)).ti,ab,kf. 16609

40 disutilit*.ti,ab,kf. 728

41 rosser.ti,ab,kf. 113

42 willingness to pay.ti,ab,kf. 10526

43 standard gamble*.ti,ab,kf. 950

44 (time trade off or time tradeoff).ti,ab,kf. 1792

45 tto.ti,ab,kf. 1652

46 (hui or hui1 or hui2 or hui3).ti,ab,kf. 2224

47 (eq or euroqol or euro qol or eq5d or eq 5d or euroqual or euro qual).ti,ab,kf. 27214

48 duke health profile.ti,ab,kf. 96

49 functional status questionnaire.ti,ab,kf. 137

50 dartmouth coop functional health assessment*.ti,ab,kf. 14

51 or/14-50 [CADTH filter for Health Utilities/Quality of Life – OVID Medline
<https://www.cadth.ca/strings-attached-cadths-database-search-filters>] 835545

52 Quality-Adjusted Life Years/ 17827

53 (quality adjusted or adjusted life year\$).ti,ab,kf. 28670

54 (qaly\$ or qald\$ or qale\$ or qtime\$).ti,ab,kf. 16934

55 (illness state\$1 or health state\$1).ti,ab,kf. 9402

56 (hui or hui1 or hui2 or hui3).ti,ab,kf. 2224

57 (multiattribute\$ or multi attribute\$).ti,ab,kf. 1590

58 (utility adj3 (score\$1 or valu\$ or health\$ or cost\$ or measur\$ or disease\$ or mean or gain or gains or index\$)).ti,ab,kf. 23388

59 utilities.ti,ab,kf. 10614

60 (eq-5d or eq5d or eq-5 or eq5 or euro qual or euroqual or euro qual5d or euroqual5d or euro qol or euroqol or euro qol5d or euroqol5d or euro quol or euroquol or euro quol5d or euroquol5d or eur qol or eurqol or eur qol5d or eur qol5d or eur?qul or eur?qul5d or euro\$ quality of life or european qol).ti,ab,kf. 21024

61 (euro\$ adj3 (5 d or 5d or 5 dimension\$ or 5dimension\$ or 5 domain\$ or 5domain\$)).ti,ab,kf. 7160

62 (sf36\$ or sf 36\$ or sf thirtysix or sf thirty six).ti,ab,kf. 29275

63 (time trade off\$1 or time tradeoff\$1 or tto or timetradeoff\$1).ti,ab,kf. 2700

64 quality of life/ and ((quality of life or qol) adj (score\$1 or measure\$1)).ti,ab,kf. 17855

65 quality of life/ and ec.fs. 11408

66 quality of life/ and (health adj3 status).ti,ab,kf. 13167

67 (quality of life or qol).ti,ab,kf. and Cost-Benefit Analysis/ 18905

68 ((qol or hrqol or quality of life).ti,kf. or ∗quality of life/) and ((qol or hrqol\$ or quality of life) adj2 (increas\$ or decrease\$ or improv\$ or declin\$ or reduc\$ or high\$ or low\$ or effect or effects or worse or score or scores or change\$1 or impact\$1 or impacted or deteriorat\$)).ab. 54525

69 Cost-Benefit Analysis/ and (cost-effectiveness ratio\$ and (perspective\$ or life expectanc\$)).ti,ab,kf. 6058

70 *quality of life/ and (quality of life or qol).ti. 70814

71 quality of life/ and ((quality of life or qol) adj3 (improv\$ or chang\$)).ti,ab,kf. 48768

72 quality of life/ and health-related quality of life.ti,ab,kf. 51276

73 models, economic/ 11597

74 or/52-73 [Filter FSF - sensitivity maximizing filter to identify HSU studies, from Arber et al, 2017 <http://dx.doi.org/10.1017/S0266462317000897>] 252309

75 13 and 51 226

76 13 and 74 102

77 75 or 76 232

78 (202304* or 2024* or 2025*).dt,ez,da,ed. [added to Medline since company's initial search in April 2023] 2581901

79 77 and 78 28

Embase for health-related quality of life – searched 15/05/25

Embase <1974 to 2025 May 14>

1 exp follicular lymphoma/ 23347

2 (((follicul* or nodular* or histiocytic*) adj3 lymphom*) or "brill symmers" or FL).ab,ti. 64745

3 non-Hodgkin lymphoma/ 72545

4 (indolent or low grade or slow growing or non aggressive).ab,ti. 147541

5 1 or 2 72369

6 3 and 4 5625

7 5 or 6 76307

8 ((second or third or fourth or later) adj4 line).ab,ti. 75634

9 (refractory or intoleran* or failure* or resistan* or recurren* or metasta* or progress* or invasive* or chemorefractory or advanced or relapse*).ab,ti. 7920803

10 ((previous* or prior or salvage) adj4 (treat* or therap* or regimen*)).ab,ti. 329883

11 refractory cancer/ or cancer recurrence/ or salvage therapy/ 331017

12 8 or 9 or 10 or 11 8121500

13 7 and 12 29226

14 socioeconomic/ 176395

15 exp Quality of Life/ 767510

16 quality of life.ti,kw. 197208

17	((instrument or instruments) adj3 quality of life).ab.	5868
18	Quality-Adjusted Life Year/	40273
19	quality adjusted life.ti,ab,kw.	29939
20	(qaly* or qald* or qale* or qtime* or life year or life years).ti,ab,kw.	51910
21	disability adjusted life.ti,ab,kw.	9114
22	daly*.ti,ab,kw.	8879
23	(sf36 or sf 36 or short form 36 or shortform 36 or short form36 or shortform36 or sf thirtysix or sfthirtysix or sfthirty six or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).ti,ab,kw.	54412
24	(sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six or shortform6 or short form6).ti,ab,kw.	3297
25	(sf8 or sf 8 or sf eight or sfeight or shortform 8 or shortform 8 or shortform8 or short form8 or shortform eight or short form eight).ti,ab,kw.	1122
26	(sf12 or sf 12 or short form 12 or shortform 12 or short form12 or shortform12 or sf twelve or sftwelve or shortform twelve or short form twelve).ti,ab,kw.	13675
27	(sf16 or sf 16 or short form 16 or shortform 16 or short form16 or shortform16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).ti,ab,kw.	77
28	(sf20 or sf 20 or short form 20 or shortform 20 or short form20 or shortform20 or sf twenty or sftwenty or shortform twenty or short form twenty).ti,ab,kw.	571
29	(hql or hqol or h qol or hrqol or hr qol).ti,ab,kw.	44813
30	(hye or hyes).ti,ab,kw.	214
31	(health* adj2 year* adj2 equivalent*).ti,ab,kw.	53
32	(pqol or qls).ti,ab,kw.	810
33	(quality of wellbeing or quality of well being or index of wellbeing or index of well being or qwb).ti,ab,kw.	992
34	nottingham health profile*.ti,ab,kw.	1730
35	nottingham health profile/	717
36	sickness impact profile.ti,ab,kw.	1309
37	sickness impact profile/	2365
38	health status indicator/	3645
39	(health adj3 (utilit* or status)).ti,ab,kw.	133245
40	(utilit* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or weight)).ti,ab,kw.	28953
41	(preference* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or instrument or instruments)).ti,ab,kw.	21754
42	disutilit*.ti,ab,kw.	1458
43	rosser.ti,ab,kw.	147
44	willingness to pay.ti,ab,kw.	15393
45	standard gamble*.ti,ab,kw.	1260
46	(time trade off or time tradeoff).ti,ab,kw.	2576
47	tto.ti,ab,kw.	2536
48	(hui or hui1 or hui2 or hui3).ti,ab,kw.	3599
49	(eq or euroqol or euro qol or eq5d or eq 5d or euroqual or euro qual).ti,ab,kw.	44883
50	duke health profile.ti,ab,kw.	125
51	functional status questionnaire.ti,ab,kw.	189
52	dartmouth coop functional health assessment*.ti,ab,kw.	14

53 or/14-52 [Economic - Health Utilities / Quality of Life - Standard - Embase. In: CADTH Search Filters Database. Ottawa: CADTH; 2022: <https://searchfilters.cadth.ca/link/18.>]

1145546

54 13 and 53 815

55 limit 54 to dc=20230401-20250515 175

56 limit 54 to dd=20230401-20250515 172

57 limit 54 to rd=20230401-20250515 97

58 55 or 56 or 57 179

25 clinicaltrials.gov records removed in Endnote, leaving 154

Single Technology Appraisal

Epcoritamab for treating relapsed or refractory follicular lymphoma after 2 or more systemic treatments [ID6338]

EAG report – factual accuracy check and confidential information check

“Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release.” (Section 5.4.9, [NICE health technology evaluations: the manual](#)).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on 4 July 2025** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as [REDACTED] should be highlighted in turquoise and all information submitted as '[REDACTED]' in pink.

Issue 1 Adjustment of HMRN dataset for COVID-19 deaths

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Pages 10 and 13 - The EAG report states that “The EAG prefers to use the COVID-unmodified data from EPCORE NHL-1 for PFS and OS whilst maintaining the company’s choice of extrapolations (log-normal) for both PFS and OS, to ensure consistency with the HMRN data, which has not been adjusted for COVID-19 deaths.”	To aid understanding and interpretation, it is important to clarify in the EAG report that zero patients died due to COVID-19 in the HMRN dataset. Therefore use of the COVID-modified data from EPCORE NHL-1 offers a consistent and like-for-like analysis that is aligned with the EAG’s current logic (i.e. to “ensure consistency with the HMRN data”). This is explained in the Company Submission on page 78. The text written by the EAG should be updated throughout to note that no COVID-related deaths had occurred in 4L+ FL in the HMRN dataset. This is likely due to the few patients who were followed-up during the COVID pandemic (n= [REDACTED] [REDACTED]%) received treatment between 2020-2021).	The current claims by the EAG are factually incorrect. The Company Submission made clear that “COVID-modified data from the EPCORE NHL-1 trial were used in the ITC to remain consistent with the absence of COVID-associated deaths in the HMRN dataset... (Page 78)”. The HMRN dataset does not include any deaths related to COVID-19 in the 4L+ FL population; therefore, it is inaccurate to state that use of the COVID-unmodified data from EPCORE NHL-1 ensures consistency with the HMRN data. In fact, the opposite is true – i.e. that using COVID-modified data ensures consistency with HMRN. This is also consistent with analyses presented as part of the Company	The HMRN data collection was between 1st September 2004 and 31st December 2021. The COVID-19 virus began circulating in the UK in early 2020, with a second wave that peaked in mid-January 2021. Although the company states there was an ‘absence of COVID-associated deaths’ (CS p. 78), these data have not been provided to the EAG. The EAG is not able to rule out the possibility of COVID-related deaths occurring within the HMRN cohort. The CS acknowledged that there are challenges with

		Submission in the CSR (Table 58). Here, the observed cases of COVID-19 mortality in the EPCORE NHL-1 trial were compared with the expected cases of COVID-19 mortality using a standardised mortality ratio (SMR), the ratio of observed to expected mortality cases, and the Poisson distribution-based Fisher's exact test. The observed number (n=) and the expected number (n=) of COVID-19 fatalities were not significantly different (SMR=). This suggests that there is not expected to be a difference in COVID-related deaths between the EPCORE NHL-1 trial and those expected in practice.	defining deaths as COVID and the EAG experts similarly considered that it is difficult to establish from death certificates when COVID was a cause of death. The EAG therefore maintains their position.
Page 93 – The EAG report states that “the EAG is concerned about the potential for COVID to have affected the HMRN cohort and so should be maintained in the EPCORE NHL-1 data for balance.”			The EAG understands that some of the HMRN population were at risk of COVID infection and hence could have incurred COVID-related deaths. It is unclear whether any COVID-related deaths did occur in this cohort. If no COVID-related deaths did occur, there is a possibility of an increased likelihood of a COVID-related death when receiving epcoritamab, which

			would not be captured if censoring. The analysis provided by the company is not adequately powered to detect whether the number of observed COVID-related deaths was significantly different to the expected number of COVID-related deaths
Page 81 – The EAG report states that “The EAG understands that the HMRN cohort was also likely impacted by COVID, and so to remove these events in one source may introduce bias to the analysis by increasing the likelihood of more negative outcomes in the HMRN group”	To aid decision-making, AbbVie suggest that the EAG report be amended to acknowledge that HMRN dataset does not include COVID-19 deaths, and therefore use of the COVID-modified data from EPCORE NHL-1 offers a consistent and like-for-like analysis that is aligned with the EAG’s current logic. Further, AbbVie request that the EAG also remove the text stating that using COVID-modified data may introduce bias into the	As per above.	The EAG is unable to verify the company’s claim that HMRN does not include COVID-related deaths. The HMRN report provided to the EAG does not mention COVID-19.

	analysis, per the logic described above. AbbVie propose an alternative text: <i>“A COVID-related death in the HMRN dataset had been defined as one where a mention of COVID had been reported on a patient’s death certificate. No COVID-deaths had been reported in █ patients with 4L+ FL from the HMRN dataset (followed-up to December 2021). The “COVID-modified” analysis presented by the Company does not include COVID-related deaths for either the EPCORE NHL-1 trial or the HMRN dataset”</i>		
Page 82. It is potentially misleading for the EAG to state their preference for the “non-adjusted COVID-19” analysis on the basis that it reflects “real-world trial conditions”. The preferred analyses should seek to	The following EAG text should be updated: <i>“The EAG consider the non-adjusted COVID-19 data for the survival analysis to be the more appropriate source of evidence, as it better reflects real-world trial conditions and avoids introducing bias by selectively censoring deaths, given the uncertainty</i>	There is an error in the current EAG text. The preferred analysis should be one that closely reflects current UK practice and not “real-world trial conditions”. The impact of COVID-19 on the EPCORE NHL-1 trial has to be considered within the context of the global pandemic environment in 2020-2022. The risk of death due to	Not a factual error.

closely reflect current UK practice.	<i>around the timing and confirmation of CR in those who have died of COVID-19.”</i> To aid clarity and understanding, AbbVie propose an alternative text: <i>“The EPCORE NHL-1 trial was conducted at the height of the Global COVID-19 pandemic. The Company argued that outcomes in the COVID-modified analysis are more generalisable to the current risk with COVID-19 in the UK. Nonetheless, the EAG consider the non-adjusted COVID-19 data for the survival analysis to be the more appropriate source of evidence, as it avoids introducing bias by selectively censoring deaths, given the uncertainty around the timing and confirmation of CR in those who have died of COVID-19”</i>	COVID-19 has been substantially reduced since the height of the pandemic – in part due to the availability and uptake of vaccines. The proposed text provides important context to avoid misinterpretation of the current risk surrounding COVID-19.	
Page 141 – The EAG report states that "Using covid-adjusted data for Epcoritamab appears inconsistent with approach	To aid clarity and improve accuracy, AbbVie suggest that the EAG report be amended to acknowledge that HMRN dataset does not include COVID-19 deaths, and therefore	As per above.	Not a factual error.

used for HRMN data which does not appear to be adjusted for COVID-19 deaths”	use of the COVID-modified data from EPCORE NHL-1 offers the most appropriate comparison with HMRN, as per the EAG’s current logic.		

Issue 2 Identifying deaths due to COVID-19

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Page 53 – Clarification on how COVID-19 deaths were assessed as the current text is inaccurate and does not consider the company’s response to clarification question A18	The following EAG text should be updated: <i>“The EAG has some reservations about this and asked in clarification A19...The company response confirms the decision criteria but does not fully report details of who made the decisions, only that evaluations and adjudications were performed by physicians.”</i> To more accurately incorporate the information shared with the EAG, AbbVie propose an alternative text: <i>“The EAG has some reservations about this and asked in clarification</i>	Factually inaccurate and does not consider the company’s response to clarification question A18.	The wording is an EAG summary of the information received (the company’s full response is available in the committee papers), however, the factual inaccuracy referring to A19 has been change to A18. Changed report to: The EAG has some reservations about this and asked in clarification A18 for details of how decisions over deaths attributable to Covid-19

	<i>A18...The company response confirms the decision criteria. COVID-19 deaths were assigned as per the protocol outlined in the main trial publication. Evaluations and adjudications (i.e. to make a decision over whether a death should be attributed to COVID-19) of cases were subsequently performed by trained physicians”.</i>		were made, and who made the decisions. The company response confirms the decision criteria but does not fully report details of who made the decisions, only that evaluations and adjudications were performed by physicians. The company also states that there are challenges with defining deaths as COVID-19 but that they took a pragmatic approach which was based on the interpretation of their own clinical experts.
Page 81 – The EAG state in their report that “COVID deaths typically mean that COVID infection was listed as being present at time of death, and was not necessarily the cause of death, and so censoring all	AbbVie request that the EAG amend this text in light of the detail provided in clarification question A18 to acknowledge that identification of COVID-19 deaths in EPCORE NHL-1 was performed per protocol and according to a stringent criteria with evaluations and adjudications performed by physicians.	The company have shared the process for identifying and reporting deaths due to COVID-19 in the EPCORE NHL-1 trial which was scientific, medically robust, and aligned with guidance from UK clinical experts (clarification question A18). Indeed, the EAG	The EAG acknowledged the details provided in A18 but maintains it’s position. However, the sentence on page 81 was amended to: “Additionally, COVID deaths were adjudicated

people in this category may bias the analysis”.		acknowledge that the company’s approach to identifying COVID-19 deaths aligned with that in the Linton et al. 2024 publication, which they state “conducted COVID-19 sensitivity analyses using stringent adjudication criteria for censoring” (page 60). Further, Section 2.6.2.1 of the Company Submission states that “Based on the clinical adjudication and review of the trial data and site investigator reports, a total of █ patient deaths were attributable to COVID-19 within the 4L+ population, of which █ occurred during the Omicron wave of the pandemic. Of the █ deaths attributed to COVID-19, █ had occurred in patients in a CR at the time of their death.”	using prespecified and physician-led criteria; however, censoring all deaths in this category may still risk introducing bias, particularly as COVID-related deaths were not similarly censored in the HMRN comparator cohort.”
Page 81 – The EAG state in their report that “COVID deaths typically mean that	In light of the required updates for Issue 1 (raised above), AbbVie propose the following text to prevent	Definition of a COVID-related death in the HMRN dataset is required to avoid the risk of	Not a factual error. The EAG were not provided with any information

COVID infection was listed as being present at time of death, and was not necessarily the cause of death, and so censoring all people in this category may bias the analysis”.	the risk of misinterpreting how a COVID-related death had been defined in the HMRN dataset: “A COVID-related death had been defined as one where COVID-19 is mentioned on a patient’s death certificate, but not necessarily the primary reason for death. When a death occurred, a medical certificate of cause of death would be registered by the patient’s physician. No COVID-related deaths were noted in the HMRN dataset (n=████ treated during the COVID-19 pandemic).”	erroneously misinterpreting updates necessitated by Issue 1 raised above.	about COVID-related deaths in the HMRN dataset, including definitions.

Issue 3 Wording around COVID-19 mortality in EPCORE NHL-1

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Page 53. The EAG Report erroneously states that in the CS, the Company adjusted for excess mortality seen during the Omicron COVID-19 wave. This had been a scenario	The following EAG text should be updated: “The CS presents results that were adjusted for excess mortality seen during the Omicron COVID-19 wave during the expansion part of the EPCORE NHL-1 study.”	The current text is factually inaccurate and could be misinterpreted. A scenario exploring a censoring approach during the Omicron wave of the pandemic had been presented at Clarification Questions and	The EAG accepts that there is a factual inaccuracy in the statement. Changed text to: The CS presents results that were adjusted to

explored at Clarification Questions.	To increase accuracy and improve efficient decision-making, AbbVie propose an alternative text: <i>“In the CS, the Company censored patients with a COVID-related mortality at the time of their death. █ of the █ patients who died due to COVID-19 did so during the Omicron wave. As such and at Clarification Questions, the Company presented a scenario whereby results were adjusted for excess mortality seen during the Omicron COVID-19 wave during the expansion part of the EPCORE NHL-1 study”.</i>	been omitted from the report. The CS and preferred base-case assumes that all COVID-19 deaths would not have occurred had it not been for the pandemic.	ensor deaths related to the COVID-19 pandemic during the expansion part of the EPCORE NHL-1 study.
Page 53 - The EAG note the possibility of non-COVID-19 (or “Other”) infection risk that may not be fully accounted for due to the competing risk of COVID-19 mortality at the height of the COVID-19 pandemic. Data from the Dose Expansion cohort, presented in the Company Submission (Table 35), have shown that	The following EAG text should be updated: <i>“In addition, there is the possibility that epcoritamab itself increases infection risk and while COVID-19 infections are lower now, there are other infections which can impact mortality.”</i>	There are available data from the Company Submission that make the existing sentence factually inaccurate without further context. One fatal TEAE linked with “Other” infections and infestations was reported at the height of the COVID-19 pandemic. In the 12+ months	This is the EAG clinical advisers opinion in relation to the sentence above stating that it is likely difficult to confirm that COVID-19 infection was the cause of death, however, this was not made clear. Wording changed to:

the risk of “Other” infection-related mortality is low. One patient died due to pseudomonal sepsis over follow-up. No “Other” infection-related mortality occurred following the height of the COVID-19 pandemic. No infection-related mortality was observed in the Dose Optimisation cohort.	To support informed and effective decision making, AbbVie propose an alternative text: <i>“In addition, there is the possibility that epcoritamab itself increases infection risk and while COVID-19 infections are lower now, there are other infections which can impact mortality. Company data presented in the CS (Table 35) show that there was one fatal TEAE linked with other infections, despite follow-up continuing until [REDACTED] when COVID-19 infection rates were lower. No infection-related mortality occurred in the Dose Optimisation cohort.”</i>	from the April 2023 DCO to the [REDACTED] DCO, and after the peak of the COVID-19 pandemic, no further deaths due to “Other” infections occurred. In the 5.7 months median follow-up from the Dose Optimisation cohort (January 2024 DCO), no deaths were attributed to any infections. The company believe that the existing sentence must be updated to reflect data on “Other” infections and the associated mortality risk following the height of the pandemic.	In addition, the EAG experts considered that there is the possibility that epcoritamab itself increased infection risk and while COVID-19 infections are lower now, there are other infections which can impact mortality.

Issue 4 Premature and inappropriate preconception of directionality of MAIC adjustments

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Page 13 – The EAG state that “counterintuitively, the MAIC adjustment resulted in hazard ratios that favoured [REDACTED] than in the unadjusted analysis, when one would expect the effect size to attenuate after adjusting, not improve”	To maintain a neutral and unprejudiced presentation of the Company Submission, AbbVie propose that the EAG amend these items of text to remove mention of an <i>a priori</i> assumption regarding the directional impact of the MAIC. The following amendments are proposed:	AbbVie recognise that the current statements by the EAG are their own opinion. However it is potentially misleading and not scientifically robust to make assumptions regarding the directionality of output based solely on the source of the data.	The EAG amended the sentence on page 13 to: “The MAIC adjustment resulted in hazard ratios that favoured [REDACTED] than in the unadjusted analysis. While the direction of change following adjustment is not always predictable, this result was not expected.”

Page 79 – The EAG report states that “the application of MAIC weights unexpectedly improved the effectiveness of epcoritamab”	Page 13 – “...~~counterintuitively~~, the MAIC adjustment resulted in hazard ratios that favoured [REDACTED] than in the unadjusted analysis, ~~when one would expect the effect size to attenuate after adjusting, not improve.~~” Page 79 – “The application of MAIC weights ~~unexpectedly~~ improved the effectiveness of epcoritamab.” Page 80 – “Finally, the EAG considers it implausible that the application of weights to a trial dataset, when matching to real-world evidence, would improve the efficacy of epcoritamab. However in the CS, clinical experts described baseline characteristics for the EPCORE NHL-1 trial as closely reflecting the fitness of patients in clinical practice or presenting with higher-risk features than seen in real world populations.”	Further, it is factually inaccurate to state that matching of a trial population to real-world evidence would result in worse outcomes for the intervention (and that anything to the contrary is “counterintuitive”) as real-world populations <i>can</i> exhibit greater baseline fitness than trial cohorts (e.g. TA1001).	The EAG amended the sentence on page 79 to: “The application of MAIC weights led to HRs that indicated [REDACTED] of epcoritamab than in the unadjusted analysis. While this is not inherently implausible, it was an unexpected result given the differences between the trial and real-world comparator populations. This direction of effect also [REDACTED] with the findings of most MAICs in the HTA process and in the literature, where adjustment typically results in [REDACTED].”
Page 80 – The EAG report states that “the EAG considers it implausible that the application of weights to a trial dataset, when matching to real-world evidence, would improve the efficacy of epcoritamab”		Further, as stated in the Company Submission (page 111), clinical experts were in consensus that the study was generalisable to clinical practice in the UK, with the fitness of the trial population either closely reflecting the fitness of patients in clinical practice or presenting with higher-risk features than seen	Not a factual inaccuracy.

		in real world populations. The current judgement of the EAG does not address feedback on the severity of the trial population that had been outlined by clinical experts.	

Issue 5 Language around MAIC

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Pages 80 and 126. The EAG states that the MAIC is “ <i>unhelpful and potentially mis-leading for decision-making purposes</i> ”. The company believe that it is for the Committee to decide if the MAIC is helpful regarding decision-making. Furthermore, the current language is not balanced nor academic.	AbbVie ask that this language is either removed or updated. For example, “the EAG considers the results of the MAIC to be uncertain.”	The company accept that the EAG has an alternative preference for informing the relative efficacy. However, the MAIC has been conducted in accordance with TSD18 and follows approaches undertaken by other companies in TA627 and TA1001. The current language is not balanced nor academic and inaccurately details the	Not factual inaccuracy.

		rationale for the EAG's preferred choice of comparison. It is not appropriate or accurate to outline one approach as unhelpful or misleading when it is aligned to the methodological practices outlined in the technical support documents and previously accepted by NICE Committees.	

Issue 6 Language around reporting of MAIC variables

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Page 77 – The EAG state that “The company commented that age and disease stage may have sufficiently correlated with ECOG and FLIPI, downplaying the importance of their omission from the analysis.”	To maintain academic and neutral language, AbbVie request that the EAG remove the word “downplaying” from this sentence and use more neutral and academic terminology, focusing solely on the factual text provided in the Company Submission and the response to Clarification Question A24.	The use of “downplaying” is factually inaccurate and suggests an intentional effort to mislead the NICE committee. The company are limited in what they can adjust for in their analyses due to data constraints from HMRN. Further, in recognition of this, the company provided sensitivity analyses (in	Sentence amended to: “The company noted that age and disease stage are components of the FLIPI score and therefore were indirectly adjusted for through inclusion of FLIPI in the analysis. As such, the company did not

		response to Clarification Question A24), and imputed values in some cases to explore the impact. Thus, this language is inappropriate.	consider their omission to substantially bias the analyses.”
	To aid clarity, AbbVie request that the EAG clarify their language around age and disease stage being “correlated” with FLIPI to reflect that FLIPI score considers these components, which are adjusted for separately within the MAIC	It is incomplete to solely state that “age and disease stage may have sufficiently correlated with ECOG and FLIPI” as in the case of FLIPI, these variables are components which contribute to the composite score.	As above.

Issue 7 Reporting of MAIC sensitivity analyses

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Page 79, Table 23. The EAG have erroneously omitted a final scenario that had been explored at Clarification Questions. The EAG have presented two of the three MAIC analyses that had been explored in the Company Submission and at	At Clarification Questions (A25; Table 10), the company presented an alternative MAIC scenario whereby patients who died due to COVID-19 during the Omicron wave had been censored. This should be accounted for in Table 23 so that the available analyses surrounding the impact of	Factual inaccuracy through omission. The EAG have erroneously omitted a final scenario that had been explored at Clarification Questions. This scenario is not reviewed, described, or critiqued elsewhere in the EAG Report. It is	The EAG agree with the proposed amendment and have added the missing scenario in Table 23. And added the following text to the preceding paragraph:

Clarification Questions. All three scenarios should be presented to avoid risk of misrepresenting the analyses that had been presented in response to Clarification Question A25.	COVID-19 in the MAIC may not be misinterpreted.	recommended that this scenario is included to avoid risk of misrepresenting the available data for decision-making.	“...and the results where the COVID-related deaths during the Omicron wave of the COVID-19 pandemic were censored”

Issue 8 Reporting of the severity modifier

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Page 119, table 47 – The EAG’s value for the proportional QALY shortfall is currently presented as a number to two decimal places.	To improve clarity during decision making, AbbVie request that the EAG update the proportional QALY shortfall so that it is presented as a proportion (percentage, %). This will ensure consistency with the proportional QALY shortfall presented by the company in the same table. Furthermore, given the poor life expectancy in this patient population and the high unmet need as detailed by the clinical experts advising the EAG, the reporting would be more balanced if the closeness of the EAG’s proportional QALY shortfall analysis to the 85%	Factual inaccuracy through omission. The current proportional QALY shortfall presented by the EAG could be misinterpreted as 0.84%. In the interest of patients, it should be reported as 84.4%.	Not a factual inaccuracy. However, the value has been amended as proposed by the company to align with company’s reporting. The EAG has also slightly amended the sentence below to emphasize the value of the proportional QALY shortfall.

	threshold is made transparent. AbbVie therefore proposes that a) The EAG's proportional shortfall is reported as 84.4% throughout and b) The EAG adds context that its shortfall is very close to the threshold of 85% for the 1.2 severity modifier.		"The proportional QALY shortfall was less than 85% (but very close i.e., 84.4%) whilst absolute QALY shortfall <12."

Issue 9 Premature judgement around overestimation/underestimation of model outcomes

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Page 9 – The EAG report states that "Approach to costing adverse events in economic model overestimates adverse events costs in comparator arm"	To aid clarity and informed decision making, AbbVie propose that the wording be amended to "Approach to costing adverse events in economic model <i>may overestimate</i> adverse events costs in comparator arm"	Due to the paucity of data surrounding incidence of adverse events for patients currently receiving 4L+ care in practice, there is no robust evidence that the company model overestimates costs for this arm. This is a premature and unfounded conclusion regarding model parameters for which there is a lack of evidence	The EAG has amended the statement as requested by the company. Similar amendment was made to issue 7 However, the EAG does not agree that the conclusions are unfounded as EAG's clinical experts' opinions

			were that the adverse events in comparator arm appeared overestimated and the EAG's experts believed it was because the source of incidence data was based on R-CHOP only. The EAG showed that weighting the incidences of AEs based on published data for O-benda, R-CHOP and R ² will lower the incidence rates, even though the impact on the ICER was [REDACTED].
Page 9 – The EAG report states that “Haematologist consultant visits slightly underestimated for Epcoritamab in the economic model”	To maintain neutral language, AbbVie propose that the wording be amended to “Haematologist consultant visits <i>may be</i> slightly underestimated for Epcoritamab in the economic model	The co/any note that clinical experts engaged during the development of the Company Submission validated the resource use assumptions presented in the Company's model. While the company recognises that the EAG's clinical experts propose different resource use estimates, it is inappropriate to conclude in absolute terms	The wording has been amended as suggested by the company. Similar amendment made to Issue 8 (page 15)

		that the model underestimates any components of healthcare resource use based on differences in clinical opinion	

Issue 10 Labelling of EAG analyses

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Page 137 – The rows demonstrating the cumulative impact of the EAG’s changes is incorrectly labelled as “EAG01 – EAG05” when the values for these analyses are performed by also applying the assumptions in EAG 06.	AbbVie request that the EAG clarify which assumptions they wish to include for these rows	Error in reporting	The text has been amended.

Issue 11 Reporting of EAG cost-effectiveness analyses

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Table 2, Table 54 and Table 55 – The EAG report the %	To improve clarity during decision making, AbbVie suggest that the EAG	While this is not a factual inaccuracy, the company’s	Both absolute change and percentage change

change in ICER compared with the company base case.	report the <i>absolute</i> difference in ICER rather than the percentage change for each analysis.	suggested approach would provide all parties with improved visibility to assess which assumptions impact the ICER such that they may exceed the willingness-to-pay threshold. This allows for improved decision making by the committee.	in ICER have been presented.
Table 2 Table 54 and Table 55 – Reporting of incremental QALYs	To improve clarity during decision making, AbbVie suggest that the EAG report the total QALYs for each arm in addition to providing the incremental QALYs.	The EAG report only incremental QALYs in their analysis rather than reporting the total QALYs for each arm; therefore, it is unclear which assumptions have impacted QALY outputs such that the ×1.2 severity modifier is no longer applied. This is particularly pertinent for this appraisal where the severity modifier is being considered.	Total QALYs in each arm have been presented.
Pages 12-15 – Consistency in how key issues are reported	To improve consistency, AbbVie suggest that the EAG limit their description of impacts of key issues on cost-effectiveness outcomes to focus solely on the direction of its impact, rather than providing subjective	The EAG describe the impact of key issues on the ICERs using adjectives which could be considered subjective and misleading.	Not a factual inaccuracy. The descriptions are based on the results of the EAG's analyses. However, as per company's request, the

	narrative around the magnitude of these differences.		EAG has edited the text to only include the direction of the impact on ICER for any key issues.
Table 55 – ICERs do not include the EAG’s correction to the company base case and instead carry this error forward throughout their reported results	To improve clarity during decision making, AbbVie suggest that the EAG re-run the analyses presented in Table 55 to consider the company-corrected base case rather than the company base case.	Factual inaccuracy	The analyses have been re-run considering the company’s corrected base case ICER.

Issue 12 Inconsistent description of key issues

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Page 12 – The EAG label Issue 2 differently on page 12 compared with the labelling in Table 1	To aid clarity, AbbVie proposes that each key issue is described consistently.	Improved clarity	The labelling for issue 2 has been updated to be consistent with labelling in table 1
Page 12 – The EAG frequently refer to COVID-19 under Issue 2; however, this is listed separately as Issue 4	To facilitate efficient decision making, AbbVie proposes that the EAG clarifies the identified issues in the minimum number of issue statements. For example, it is currently unclear how the issues regarding COVID-19 in Issue 2	Improved clarity	Not a factual inaccuracy. Covid-19 deaths was one of the issues that contributed to the

	differ from those in Issue 4. AbbVie recommend that these are consolidated in one Issue (i.e. Issue 4).		evidence uncertainty (amongst the other factors highlighted under key issue 2). The EAG considers that use of covid-adjusted data is a key issue that needs to be considered on its own and have made it clear under issue 2 that this is described in more detail as a separate issue. Therefore, the EAG prefers to keep the 2 issues separate.

Issue 13 Reference of data availability from data cuts

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Page 12 – The EAG state in their report that “There are limitations with the epcoritimab study. EPCORE NHL-1 is an ongoing, single-arm, open-label trial. The data are from subgroups relating to	To increase clarity for the committee, AbbVie ask that the EAG clarify this statement to make clear that this statement refers to the 3L+ subgroup rather than the 4L+ subgroup on which the company focuses its submission. All data that the company submitted are relevant to the proposed position	The existing statement made by the EAG is a factual inaccuracy and could potentially be misleading. Increased clarity here will provide improved transparency for the committee around the	The EAG accept that most of the missing data below has been signposted or provided by the company the EAG not all of these could be verified with the sources

number of prior lines of treatment and some data are not available at the latest data cuts”	for epcoritamab (i.e. 4L+ FL). The EAG should make it clear that they have not been able to validate data and outcomes for populations outside of the positioning for epcoritamab. Finally, this statement should make specific mention that the survival data used within the cost-effectiveness modelling is all from the latest available data cut of EPCORE NHL-1 – i.e. the [REDACTED].	positioning of epcoritamab in 4L+ FL and the availability of data.	available. Therefore text changed to: The data are from subgroups relating to number of prior lines of treatment and some data from the latest data cuts could not be validated.

Issue 14 Description of the EPCORE NHL-1 participation criteria and the population

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Page 12 – The EAG state in their report that “These limitations combined with heterogeneity in the patient population raise questions about the generalisability of the findings to the broader population of patients with relapsed/refractory FL in routine clinical practice”.	To aid clarity, AbbVie ask that the EAG revise their current statement. It should be noted that the population that epcoritamab is positioned for is a clearly defined population with similar characteristics. Almost all patients in 4L+ FL present with high-risk characteristics. This is reflected in the anticipated survival for this group of patients, whereby the median OS has been shown to be [REDACTED] months with existing care in the UK.	The statement made by the EAG is a factual inaccuracy.	Not a factual inaccuracy this is EAG opinion about generalisability to UK patients, as noted in the ‘what additional evidence or analyses might help to resolve the key issue’.

Page 36 – The eligibility criteria for the EPCORE NHL-1 FL cohort stated as “Eligible patients are ≥ 18 years old, who were relapsed, progressive and/or refractory following treatment with anti-CD20 monoclonal antibody, having exhausted all previous lines of treatment and have an ECOG PS score 0 – 2”	The eligibility criteria is not described accurately and should read ‘Eligible patients are ≥ 18 years old, who had at least two previous lines of therapy (including an anti-CD20 monoclonal antibody and an alkylating agent or lenalidomide) treatment and have an ECOG PS score 0 – 2.	For clarity participants were not required to have exhausted all previous lines of treatment	The EAG accepts that this summary does not list all of the eligibility criteria, however the EAG notes that Table 10 inclusion criteria (and trial protocol) state that “Patients must have exhausted or are ineligible for all standard therapeutic options”. The EAG notes that the additional details requested here are also missing from CS Table 10 (although can be found in the trial protocol). Text changed to Eligible patients are ≥ 18 years old, who were relapsed, progressive and/or refractory to at least 2 prior lines of treatment (including anti-CD20 monoclonal antibody), having exhausted or are

			ineligible for standard treatment options and have an ECOG PS score 0 – 2
Page 38 and 39 - Population of EPCORE NHL-1 trial that states patients are exhausted or ineligible for standard care. This was not part of the eligibility criteria for the study.	For increased accuracy, this should be amended as outlined for EAG Issue 1 to clarify patients must have relapsed or refractory disease and have received at least two previous lines of therapy (including an anti-CD20 monoclonal antibody and an alkylating agent or lenalidomide)	Factual inaccuracy	Not a factual inaccuracy. As above, this is a stated inclusion criteria for EPCORE NHL-1 in CS Table 10 and the study protocol.

Issue 15 Description of primary endpoint from EPCORE NHL-1

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Page 39 – The description of the primary endpoint ORR in the EAG report is incorrect: “ORR: The proportion of patients who achieved BOR of CR or CRi, determined by Lugano criteria as assessed by independent review committee (IRC)”	For increased accuracy, AbbVie propose that the EAG amend their description to the below: “ORR determined by LUGANO criteria to be defined as: the proportion of patients who reached a best overall response of partial response or complete response at any time.”	Factually inaccurate. For clarity patients with a BOR of PR were included in ORR, determined by LUGANO criteria. CRi is not included in LUGANO criteria.	The EAG accepts there was some factual inaccuracy in this statement. However, CS Table 10 and trial protocol state ORR was IRC-assessed. Therefore amended as follows: ORR determined by LUGANO criteria and

			assessed by IRC, defined as: the proportion of patients who reached a best overall response of partial response or complete response at any time.

Issue 16 Error in describing the dosing regimen for epcoritamab

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Page 37 – The EAG state that “Participants received epcoritamab subcutaneously at 48 mg in 4-week cycles (i.e., 28 days) at varying doses”	To aid clarity, AbbVie ask that the EAG remove “48 mg” from this sentence and include the relevant dosages for the step-up dosing and 48 mg dosing separately in the subsequent bullet points	It is unclear to state a dosage of 48 mg followed by stating “varying doses”. This amendment will provide improved clarity around epcoritamab dosing and reduced potential for misunderstanding	Thank you, we have removed 48mg from this sentence and added the doses to the subsequent bullet-points. Text changed to: Participants received epcoritamab subcutaneously in 4-week cycles (i.e., 28 days) at varying doses as follows: • Cycle 1: dose escalation, Day 1: 0.16 mg, Day 8: 0.8 mg, Day

			15: 48 mg (Dose Expansion Part) or Cycle 1 Day 1: 0.16 mg, Day 8: 0.8 mg, Day 15: 3 mg, Day 22: 48 mg (Dose Optimisation Part) • Cycle 2-3: Days 1, 8, 15, and 22 (once weekly) 48 mg • Cycle 4-9: Days 1 and 15 (every 2 weeks) 48 mg • Cycles 10 to progressive disease (PD), unacceptable toxicity, or end of trial: Day 1 (every 4 weeks) 48 mg
Page 90 – The EAG state that “epcoritamab is administered as a subcutaneous injection for up to ten cycles until disease progression, toxicity or withdrawal of consent”	For increased accuracy, AbbVie ask that the EAG remove the text “up to 10 cycles” as this is factually inaccurate.	Inaccurate description of dosing regimen for epcoritamab.	Amended

Issue 17 Reporting of baseline characteristics

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Table 8 – The EAG state that the number of patients receiving prior radiotherapy is not reported for the 4L+ EPCORE NHL-1 expansion phase; however, this data was included in the TLF file shared with the EAG	For increased accuracy, AbbVie request that the EAG correct this cell to read “26 (32.1%)”	Data has been labelled as ‘Not reported’ but was provided to the EAG as part of the Company Submission	The EAG thank the company for pointing these data out, we note the data weren’t reported in the main CS or CS appendices but we accept they were overlooked in the multiple pdfs provided by the company but were not cited by the company in document B or appendices. Amended
Table 8 – The EAG state that the number of patients receiving prior rituximab + lenalidomide is not reported for the 4L+ EPCORE NHL-1 expansion phase; however, this data was included in the TLF file shared with the EAG	For increased accuracy, AbbVie request that the EAG correct this cell to read “25 (30.9%)”	Data has been labelled as ‘Not reported’ but was provided to the EAG as part of the Company Submission	Amended

Table 8 - The EAG state that the numbers of patients receiving prior radiotherapy and stem cell transplant were not reported for the 4L+ EPCORE NHL-1 optimisation phase; however, this data was included in the TLF file shared with the EAG	For increased accuracy, AbbVie request that the EAG correct this stem cell transplant value to read “9 (22.0%)” and the radiotherapy value to read “17 (41.5%)	Data has been labelled as ‘Not reported’ but was provided to the EAG as part of the Company Submission	The EAG has checked the documents provided but has been unable to find the data stated by the company. For completeness, the EAG has added the data provided by the company to Table 8. And a footnote has been added to Table 8 stating: ‘provided by the company at FAC.’
Table 8 - The EAG state that the numbers of patients receiving prior CAR-T therapy in the 3L+ EPCORE NHL-1 expansion phase is 5%	For increased accuracy, AbbVie request that the EAG correct this value to 4.7%, aligned with the TLF file shared with the EAG for consistency of reporting decimal places	Inconsistent rounding of decimal places	Not a factual error. The footnote for this column in the EAG Table states that data were obtained from Linton 2024, where it is reported as 6 (5%). These data were extracted prior to the company providing additional data at Clarification, and as they were not missing they were not looked for.

Page 45. The EAG states that the characteristics of COVID-censored patients had not been detailed. These were presented by the Company at Clarification Questions (Appendix 1).	The following EAG text should be updated: <i>“The EAG notes that characteristics of censored patients (e.g., those receiving new anti-lymphoma therapy or affected by COVID-related mortality) were not detailed, thus limiting ability to fully assess the impact of incomplete follow-up.”</i> For increased accuracy, AbbVie propose an alternative text: <i>“The EAG notes that some characteristics of censored patients (e.g., those receiving new anti-lymphoma therapy) were not detailed, thus limiting ability to fully assess the impact of incomplete follow-up. Details of characteristics for COVID-censored patients were presented by the Company at Clarification Questions (Appendix 1) and were described in response to Question A25.”</i>	The current text is factually inaccurate. Characteristics for patients who died due to COVID-19 were presented in Appendix 1 of the response document for Clarification Questions. These are important data for understanding the risk of mortality with COVID-19.	Thank you, we have amended this as proposed.
Page 74 - Misdefining of patients with double-refractory disease	Patients with double-refractory disease should be defined as “patients who did not respond to both anti-CD20 and an	Factual inaccuracy	Amended as requested.

	alkylator”, NOT patients with follicular lymphoma with ≥ 2 lines of prior treatment.		
Page 77, Table 22 – The row for “Double refractory to anti-CD20 and alkylating agents, regardless of two treatments being in the same or different treatment lines” should not be listed under the POD24 subheading row as these are clinically different variables	To aid clarity, AbbVie request that the EAG make the difference between POD24 and double refractory disease clearer in Table 22	This is currently at high risk of being misinterpreted	Amended as requested.

Issue 18 Reporting of efficacy outcomes

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Table 8 – The EAG state that the number of patients achieving overall response and complete response in the 3L+ expansion phase of EPCORE NHL-1 is not reported; however, this	To facilitate effective decision making, AbbVie request that the EAG correct these cells as below: ORR: “ [REDACTED] ” CR: “ [REDACTED] ”	Data has been labelled as ‘Not reported’ but was provided to the EAG as part of the Company Submission	The EAG thank the company for pointing these data out, we note the data weren’t reported in the main CS or CS appendices, and the EAG accepts they were overlooked in the

value is provided in the TLF file shared with the EAG.			multiple pdfs that were provided by the company but were not cited by the company in document B or appendices. Changed data
Page 56 - The EAG report contains the following text “In the 3L+ subgroup ■■■% and ■■■% achieved CR and PR respectively”	AbbVie note that the EAG have reported a PR value from a previous data cut for EPCORE NHL-1, rather than the most recent ■■■ DCO. The company request that the EAG amend this text to include the latest available data, as below: “In the 3L+ subgroup ■■■% and ■■■% achieved CR and PR respectively”	Latest available data cut	Amended
Table 13 – The EAG report states response outcomes from the expansion part of 3L+ EPCORE NHL-1 is not reported; however, this data is provided in the TLF file shared with the EAG.	To facilitate effective decision making, AbbVie request that the EAG update these values as follows: ORR: ■■■■■■■■■■ CR: ■■■■■■■■■■ PR: ■■■■■■■■■■	Data has been labelled as ‘Not reported’ but was provided to the EAG as part of the Company Submission	Amended
Table 14 – The EAG have erroneously reported follow-up values for COVID-	To maintain accuracy and facilitate effective decision making, AbbVie ask that the EAG amend Table 14 to	Factual inaccuracy.	Amended as requested

modified data as COVID-unmodified data	include the following follow-up durations for the COVID-unmodified population, in line with the data reported in the Company Submission Appendices and provided TLF file: PFS: [REDACTED] OS: [REDACTED]		
Page 64 – The EAG state that a CSR for the Expansion 4L+ subgroup was not provided. This could imply that a CSR had been available, though was not shared.	The following EAG text should be updated: <i>“A CSR for the Expansion 4L+ subgroup was not provided with the original CS, however an abbreviated report of relevant tables was provided in response to Clarification A4 and the EAG has checked data where available.”</i> For increased transparency to the committee, AbbVie propose an alternative text: <i>“A CSR for the Expansion 4L+ subgroup was not provided with the original CS as no CSR had been produced for the 4L+ FL subgroup. However an abbreviated report of relevant tables was provided in</i>	This is a misrepresentation of the company response to Clarification Question A4 that is likely to lead to a factual inaccuracy. The sentence on the availability of data for the 4L+ FL subgroup has been updated to avoid any implication that a CSR is available for this population.	A CSR for the Expansion 4L+ subgroup was not provided with the original CS, however the company stated they do not have a CSR for this subpopulation and an abbreviated report of relevant tables was provided in response to Clarification A4. The EAG has checked data where available.

	<i>response to Clarification A4 and the EAG has checked data where available.”</i>		

Issue 19 Reporting of clarification questions associated with time to next treatment

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Page 63 – The EAG state that “The EAG sought clarification on this issue (Clarification Questions A19 and A20).”	AbbVie asks that the EAG remove this sentence and updates the subsequent sentences in the paragraph. Clarification Questions A19 and A20 refer to “new anti-lymphoma therapies” in Tables 18, 19, 20, and 22 of the Company Submission. There is no request from the EAG for clarification on the discrepancy between “new anti-lymphoma therapies” (Table 22) and Time to Next Treatment (Table 23).	Factual inaccuracy.	The EAG has removed this sentence and amended the subsequent sentences.

Issue 20 Reporting of safety outcomes

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response																																																
Table 17 – The company notice that there are empty cells within this table even though data for these inputs are available from documents shared with the EAG.	To provide complete and accurate information to the committee, AbbVie request that the EAG update the table as illustrated below: <table> <tr> <th></th><th colspan="2">Expansion Part^a</th><th>Optimisation Part^b</th></tr> <tr> <th>Grade 3 or 4 TEAEs^c</th><th>4L+ (N=81)_c</th><th>3L+ (N = 128)_c</th><th>3L+ (N = 86)_c</th></tr> <tr> <td>≥1 grade 3 or 4 TEAE</td><td>■</td><td>■</td><td>■</td></tr> <tr> <td>Anaemia</td><td>■</td><td>■</td><td>■</td></tr> <tr> <td>COVID-19</td><td>■</td><td>■</td><td>■</td></tr> <tr> <td>COVID-19 pneumonia</td><td>■</td><td>■</td><td>■</td></tr> <tr> <td>Leukopenia/Leukocytopenia</td><td>■</td><td>■</td><td>■</td></tr> <tr> <td>Lymphopenia</td><td>■</td><td>■</td><td>■</td></tr> <tr> <td>Lymphocyte count decreased</td><td>■</td><td>■</td><td>■</td></tr> <tr> <td>Neutropenia</td><td>■</td><td>■</td><td>■</td></tr> <tr> <td>Neutrophil count decreased</td><td>■</td><td>■</td><td>■</td></tr> <tr> <td>Pneumonia</td><td>■</td><td>■</td><td>■</td></tr> </table>		Expansion Part ^a		Optimisation Part ^b	Grade 3 or 4 TEAEs ^c	4L+ (N=81) _c	3L+ (N = 128) _c	3L+ (N = 86) _c	≥1 grade 3 or 4 TEAE	■	■	■	Anaemia	■	■	■	COVID-19	■	■	■	COVID-19 pneumonia	■	■	■	Leukopenia/Leukocytopenia	■	■	■	Lymphopenia	■	■	■	Lymphocyte count decreased	■	■	■	Neutropenia	■	■	■	Neutrophil count decreased	■	■	■	Pneumonia	■	■	■	Table is currently incomplete despite data being available to the EAG.	The EAG note that the Table is accurate as the footnote states it was reporting events occurring in ≥5% of Expansion 4L+ and 3L+; ≥2% of C1-OPT 3L+', as per the cited sources. For completeness the EAG has checked the various pdf documents provided, which have thousands of pages, but has been unable to find all of these data stated by the company.
	Expansion Part ^a		Optimisation Part ^b																																																
Grade 3 or 4 TEAEs ^c	4L+ (N=81) _c	3L+ (N = 128) _c	3L+ (N = 86) _c																																																
≥1 grade 3 or 4 TEAE	■	■	■																																																
Anaemia	■	■	■																																																
COVID-19	■	■	■																																																
COVID-19 pneumonia	■	■	■																																																
Leukopenia/Leukocytopenia	■	■	■																																																
Lymphopenia	■	■	■																																																
Lymphocyte count decreased	■	■	■																																																
Neutropenia	■	■	■																																																
Neutrophil count decreased	■	■	■																																																
Pneumonia	■	■	■																																																

	Thrombocytopenia	■	■	■		Therefore no change made.
	Hyperglycaemia	■	■	■		
	Hypokalaemia	■	■	■		

Issue 21 Description of treatments in the HMRN dataset

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Table 20 – The EAG provide an incomplete list of treatments used by patients with 4L+ FL in the HMRN dataset.	The following treatments should be added to those listed by the EAG: ■	The current list of treatments in the HMRN dataset is incomplete and factually inaccurate.	The EAG has added ■ but note that ■ was not used in 4L+

Issue 22 Description of MAIC baseline characteristics

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Page 76 – The EAG have left cells blank in Table 21 for FLIPI inputs where data are not reported	The EAG should populate these cells with “NR” for completeness and consistency with the rest of the table.	Consistency and completeness.	Proposed amendment added to table.
Page 78 – The EAG report states that “There were no differences between the other TEMs when comparing the estimated 95% CIs”	For increased clarity, AbbVie propose that the EAG amend this text to “There were no statistically significant differences between the other TEMs”	This restructured sentence better reflects the differences in numerical means, whilst retaining the EAG’s point of there being no statistically significant difference when considering 95% confidence intervals.	Proposed amendment added to text.

Issue 23 Description of MAIC variables

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Page 74 – The EAG state that “Key variables such as race, ethnicity, BMI, renal and hepatic function were not reported in the HMRN.”	To accurately reflect the extent of clinical input, AbbVie request that the EAG remove the word “key” from this sentence.	There is no evidence from clinical engagement, either reported by the EAG or the company, that these constitute “key” variables in	Agree with proposed amendment.

		R/R FL. Further, these variables have not been highlighted as “key” in prior NICE appraisals for this indication.	
Page 77, Table 21 – Prior radiotherapy is labelled as being included in the MAIC. This is not accurate	To more accurately reflect the MAIC methodology, AbbVie request that the EAG restructure this subsection of Table 21 to state that radiotherapy was not included as a matching variable in the MAIC	Inaccurate description of MAIC methodology	Amended in Table 21. The EAG would like to clarify the formatting issue for the last column this table made it look like radiotherapy was included in the MAIC. This was not the EAG’s intention.
Page 78 – In the paragraph beginning “prior to matching...” the EAG do not provide a balanced comparison of the baseline characteristics for EPCORE NHL-1 and HMRN	To aid clarity, AbbVie request that the EAG acknowledge that the vast majority of patients in EPCORE NHL-1 (85.2%) also had advanced disease	Improved clarity to support the committee with their decision making.	The EAG amended the sentence for clarity by adding the percentage with advanced-stage disease. “The percentage of patients in HMRN with advanced-stage disease (stage 3-4) was [REDACTED] than in EPCORE NHL-1 ([REDACTED] vs [REDACTED], respectively).”

Issue 24 Wording around suitability for best supportive care

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Page 25 – The EAG state that “The EAG clinical experts considered that some people at 4L+ who would not be fit enough for chemotherapy would be eligible for epcoritamab treatment and that therefore, the exclusion of BSC as a comparator is not appropriate.”	AbbVie asks that the EAG expand on the wording in the report. It is unclear whether the EAG clinical experts would provide BSC to patients who are not fit for chemotherapy. If BSC would not be provided to patients who are not fit enough for chemotherapy, then it is unlikely to be an appropriate comparator in a world without epcoritamab.	The current text reported by the EAG requires further expansion to prevent misinterpretation of the feedback from clinical experts.	The EAG experts considered that BSC would be provided to those not fit enough for chemotherapy. Amended text: The EAG clinical experts considered that some people at 4L+ who would not be fit enough for chemotherapy would be eligible for epcoritamab treatment instead of receiving BSC and that therefore, the exclusion of BSC as a comparator is not appropriate
Page 91 – The EAG state that “The company has not considered best supportive care as a comparator as included in NICE scope	To aid clarity, AbbVie ask that the wording of this text be amended to “The company has not considered best supportive care as a comparator as included in NICE scope because it	As currently written, the text presents an inaccurate description of the rationale for excluding best supportive care presented in the company	The text has been amended as follows:

because it is expected that patients in the 4L+ are not fit enough for an active intervention...” The company believe that this wording implies that patients at 4L+ generally would not be fit enough for an active intervention; however, the company’s rationale for excluding BSC as a comparator is that patients who would receive BSC would not be considered fit enough to be eligible for an active intervention such as epcoritamab.	is expected that patients who would receive BSC would not be considered fit enough to be eligible for an active intervention such as epcoritamab”.	submission. Further, the text is at risk of misinterpretation which could inadvertently mislead committee members into drawing inaccurate conclusions.	The company has not considered best supportive care as a comparator as included in NICE scope because it is expected that patients who would receive BSC would not be considered fit enough to be eligible for an active intervention such as epcoritamab. Clinical advice to the EAG indicates BSC should be a comparator because some patients at 4L+ who are not fit enough for chemotherapy would be eligible for therapy with epcoritamab instead of BSC.

Issue 25 Description of background mortality

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Page 93 – The EAG state that “The company submission states that the overall survival modelling is described as incorporating background mortality by not permitting the modelled hazard rate to fall below the age and sex matched population of the UK. The EAG notes that the implementation of background mortality in the model does not exactly match this description and instead represents a relative survival approach where the impact of background mortality is applied in addition to trial mortality. If the parametric models have not accounted for background mortality when fitted then it is likely that the life-years, and so QALYs, for	To more accurately reflect the information included in the Company Submission, AbbVie request that the text “If the parametric models have not accounted for background mortality when fitted then it is likely that the life-years, and so QALYs, for both arms are slightly underestimated.” be removed from the EAG report as it does not consider the methodology implemented within the analysis.	The company note that that the approach to incorporating background mortality is described fully in Section 3.3.4 of the Company Submission, which states that the background mortality is applied <i>in addition</i> to trial mortality via an internal additive approach. This ensures that OS of patients within the model does not exceed the survival of an age- and sex-matched UK population. Therefore, the text in the EAG report is not relevant and may lead the committee into reaching inaccurate conclusions.	The following text has been removed as requested. “If the parametric models have not accounted for background mortality when fitted then it is likely that the life-years, and so QALYs, for both arms are slightly underestimated.”

both arms are slightly underestimated.”			

Issue 26 Probabilistic sensitivity analysis

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Page 120 – The EAG state that “One thousand simulations were performed for the PSA, allowing values to be randomly drawn for each variable, for every simulation”	To aid clarity and understanding, AbbVie ask that the EAG clarify that values for each parameter were derived from distributions selected using published recommendations, rather than referring to “random” values being drawn.	Improved methodological transparency	The text has been amended as follows: “In line with PSA methodology, each uncertain parameter in the model was represented as a probability distribution, based on published recommendations. One thousand simulations were performed for the PSA, allowing values to be drawn at random from each probability distribution, for every simulation”

Page 122 Figure 8 – The EAG have included a scatter plot showing the incremental discounted costs and QALYs between epcoritamab and current 4L+ from iterations of the PSA. However, the figure includes a legend which could impact interpretation of the figure.	To aid clarity, AbbVie propose that the EAG remove the legend from this figure as it may otherwise be confusing that there are no iteration results for epcoritamab.	Improved clarity	The figure has been amended as requested.

Issue 27 Important typographical and formatting errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Pages 8, 12, 25, 98 – Throughout the EAG report there are instances where 'epcoritamab' is misspelled (e.g. 'epcoritimab' and 'epicoritamab')	AbbVie proposes that these typographical errors be corrected to 'epcoritamab' throughout the report	Typographical errors	Spelling error corrected
Page 9 – The pivotal trial for epcoritamab is presented as 'EPCO NHL-1'	AbbVie proposes that this be corrected to 'EPCORE NHL-1'	Typographical error	Typographical error has been amended

Page 72 – The EAG state that patients from EPCORE NHL-1 “included a more selectively defined group (4+ prior therapies)”. This is factually inaccurate as this would consider a 5L+ population, rather than the 4L+ target population in the appraisal. The HMRN dataset is also presented inaccurately; “HMRN included patients with 3+ lines of therapy”. This would imply that the HMRN dataset includes patients in 3L+ FL.	AbbVie proposes the following update to the EAG text: <i>The patient populations may also differ due to the inclusion criteria. EPCORE NHL-1 included a more selectively defined group (4+ prior therapies and relapsing remitting (R/R) disease), whereas the HMRN included patients with 3+ lines of therapy, potentially capturing a broader and more heterogeneous group – though the MAIC included the 4L+ patients in HMRN. Treatments received in the HMRN report were also more varied with no defined standard comparator, compared to EPCORE NHL-1 which used epcoritamab as the only treatment option.</i> AbbVie proposes an alternative text: <i>The patient populations may also differ due to the inclusion criteria. EPCORE NHL-1 included a more selectively defined group (3+ prior lines of therapies (4L+) and relapsing remitting (R/R) disease), whereas the HMRN included patients with 3+ prior lines of</i>	Typographical error resulting in a factual inaccuracy.	Typographical error has been amended

	<i>therapy (4L+), potentially capturing a broader and more heterogeneous group – though the MAIC included the 4L+ patients in HMRN. Treatments received in the HMRN report were also more varied with no defined standard comparator, compared to EPCORE NHL-1 which used epcoritamab as the only treatment option.</i>		
Page 76, table 21 – The value for POD24 to CIT in 1L FL (■■■%) is incorrect	■■■ patients had CIT in 1L FL and ■■ had a progression, transformation, or relapse event within 24 months of initiating 1L CIT. AbbVie proposes that the EAG update the value in table 21 to ■■ (■■■%).	Typographical error	The EAG has made it clearer in the table that this is ■■■ patients who had POD24.
Page 78 – The list of treatment effect modifiers includes an incorrect variable: “prior lines of therapy >4”	AbbVie proposes that this is corrected to “prior lines of therapy ≥ 4 ”	Typographical error	Amended as requested.
Page 78, table 22 – The table header is formatted with a black background. This hides the header text in one of the table columns.	AbbVie proposes that the colour of the table header is changed so that all column headers are visible.	Formatting error	Amended as requested.

Page 79 – The EAG have included a rounding error in the EPCORE NHL 1 (pre-MAIC), Complete response [odds ratio (95% CI)] cell	AbbVie proposes that the EAG amend the text from “ [REDACTED] ” to “ [REDACTED] ”	Rounding error	Amended as requested.
Page 92 – Obinutuzumab is incorrectly written as “Obinutusumab”	AbbVie proposes that this be corrected to “obinutuzumab”	Typographical error	Typographical error corrected
Page 98 – The EAG report incorrectly refers to best supportive care when, from context, it is assumed that the EAG intend to refer to the current 4L+ care treatment basket	AbbVie proposes that the existing text “the mean post-progression survival for epcoritimab is far in excess of the equivalent time for BSC” be amended to “the mean post- progression survival for epcoritamab is far in excess of the equivalent time for current 4L+ care ”	Typographical errors	Amended as requested

Incorrect Confidentiality Markings

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG Response
EAG report, pages 8, 11, 26, 27, 32, 82, 142	All references to the UK marketing authorisation (MA) of epcoritamab are currently redacted	Epcoritamab has now received UK MA. Previously confidential regulatory information does not need to be redacted now.	Marking was correct at time of submission of report. However, all confidentiality markings are now amended as requested.
EAG report, Table 8	Baseline characteristics are currently redacted	Baseline characteristics can be unredacted.	Amended as requested
EAG report, page 57	Incorrect marking of commercial data. The company request that the EAG amend the text as illustrated right.	The company request that the EAG amend the text as follows: “The median DOR for the 4L+ FL cohort, as assessed by IRC using Lugano criteria, was [REDACTED] at a median follow-up of [REDACTED].” “The Kaplan-Meier plot presented by the company, shown in Figure 1, shows how the curve plateaus at [REDACTED].”	Amended as requested

EAG report, page 58	Incorrect marking of commercial data. The company request that the EAG amend the text as illustrated right.	The company request that the EAG amend the text as follows: “The median DOCR for patients with 4L+ FL was NR at a median follow-up of [REDACTED]. Among the [REDACTED] complete responders, [REDACTED] experienced an event while the remaining were censored. The company did not present a Kaplan-Meier plot for this outcome, however the percentages of patients remaining in response was presented in CS Table 18. At 18 months, [REDACTED]% of patients remained in complete response. From 24 months onwards this proportion [REDACTED], again suggesting that a large proportion of patients who achieve a complete response may sustain it for a prolonged period.”	Amended as requested
EAG report, pages 58-59	Incorrect marking of commercial data. The company request that the EAG amend the text as illustrated right.	The company request that the EAG amend the text as follows: “Median PFS based on IRC assessment for 4L+ FL was [REDACTED] months, with a median follow-up of [REDACTED] months. Of the 81 patients, [REDACTED] ([REDACTED]%) experienced a PFS event (progression or death), while the remaining were censored. Censoring was primarily due to data cut-off ([REDACTED]%), followed by initiation of new anti-lymphoma therapy ([REDACTED]%) or other reasons ([REDACTED]%). KM estimates showed that [REDACTED]% of patients remained progression-free at	

		6 months, eventually plateauing at █% from 30 months onwards. █ was recorded as having progressed at the time of a COVID-related death, and █ of the █ COVID-19 deaths occurred in patients who were in CR, which, according to the company suggests that these patients would likely have had extended PFS if not for COVID-19.”	
EAG report, page 59-60	Incorrect marking of commercial data. The company request that the EAG amend the text as illustrated right.	The company request that the EAG amend the text as follows: “As of the █ data-cut, █ of the 81 4L+ FL patients had died, with a median follow-up of █. Median OS was █, indicating that █. The estimates from the KM plot show high survival in early follow-up, with █ of patients alive at 18 months and █ alive at 36 months. The company adjusted the OS results to account for COVID-19 deaths as outcomes in EPCORE NHL-1 were recorded during the COVID-19 pandemic. A total of █ deaths were clinically adjudicated, by the company’s experts, as attributable to COVID-19, of which █ occurred during the Omicron wave, and █ of these █ patients were in CR at the time of death.”	Amended as requested

EAG report, page 62	Data from FACT-Lym scores are not marked as confidential, contrasting with the markings in the company submission.	The company request the following amendment: "Mean change from baseline to end of treatment was [REDACTED]."	Amended as requested
EAG report, page 64	The EAG has not redacted the data cut for the latest readout of EPCORE NHL-1	The company request the following amendment to the footnote of Table 15: "The EAG was unable to verify data for the 3L+ subgroup derived from the [REDACTED] data cut, as the available CSR was based on the 2023 data cut."	Amended as requested
EAG report, pages 78 (table 22)	The EAG has redacted the baseline characteristics for epcoritamab in 4L+ FL. These had not been redacted in the company submission.	These figures can be unredacted.	These had been redacted based on company's initial submission (11/04/2025). However, the baseline characteristics for Epcoritamab are now unredacted
EAG report, pages 79, 140	The EAG has marked the ESS for the company's preferred MAIC (40) as confidential. This can be unredacted in line with the updated redaction markings shared by the company on 25 April 2025.	This number can be unredacted	Amended as requested

EAG report, pages 89, 90, 105	The EAG has marked the N numbers for EPCORE NHL-1 participants as confidential.	These numbers can be unredacted for consistency with the company submission and remainder of the EAG report	Amended as requested
EAG report, page 91	The proportions for constituents of the HMRN sub-baskets are not redacted in the main body of the report. As HMRN are the owners of this data and they consider this to be commercially sensitive, The company ask that the EAG redact this data in line with the company submission.	The company ask that the text be amended as follows: “For example, in the R-chemotherapy sub-basket, █% of patients received R-bendamustine, followed by R-CHOP (█%) and R-GDP (█%), the company chose R-bendamustine to represent the sub-basket in the current 4L+ care basket”	Amended as requested
EAG report, page 97	Outcomes from the HMRN dataset are not redacted. As above, HMRN are the owners of this data and they consider this to be commercially sensitive, Therefore, The company ask that the EAG redact this data in line with the company submission.	The company ask that the text be amended as follows: The resulting estimates of 3-year survival from the company’s approach is noticeably below what was observed from the HMRN follow-up (PFS = ~█%; OS = ~█%)” Consistent with this, the company ask that the “HMRN PFS” and “HMRN OS” columns in Table 27 also be marked as confidential.	Amended as requested

EAG report, page 100	Values in the below text can be unredacted in line with the updated redaction markings shared by the company on 25 April 2025: “The intercept and the health state coefficients obtained were 0.800 and 0.019 respectively with an insignificant p-value of 0.546. An estimated utility value of 0.800 for PFS and 0.819 for PD (Table 31) were obtained.”	Values can be unredacted	Amended as requested
EAG report, page 101	Values in Table 31 and Table 32 can be unredacted in line with the updated redaction markings shared by the company on 25 April 2025	Values can be unredacted	Amended as requested
EAG report, page 100	The utility value (0.800) can be unredacted in line with the updated redaction markings shared by the company on 25 April 2025	Values can be unredacted	Amended as requested
EAG report, page 176	Incremental costs in probabilistic sensitivity analysis be redacted	Incremental costs in Table 49 should be marked confidential	Amended as requested

EAG report, page 130	Values in Table 52 should be redacted to prevent reconstruction of the model	Values in Table 52 should be marked confidential	Amended as requested
EAG report, page 134	Base case utility values applied should be marked as confidential as they are based on data regarding complete response rate, which is considered confidential	The following values should be marked confidential: Epcoritamab PFS: [REDACTED] Current 4L+ PFS: [REDACTED] PD: [REDACTED]	Amended as requested

Epcoritamab for treating relapsed or refractory follicular lymphoma after 2 or more systemic treatments [ID6338]

External Assessment Group (EAG) report: Factual Accuracy Check Addendum

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1 Introduction

This addendum summarises the key issue “*Disparity in the EAG modelling of COVID-unmodified survival data*” highlighted by the company (post initial factual accuracy check), followed by the EAG response. It also contains updated cost-effectiveness analyses. A cPAS version of these updated analyses is provided separately.

1.1 *Digitisation and parameterisation of COVID-unmodified outcomes*

Company:

The EAG’s digitisation and thus parameterisation of both the COVID-unmodified OS and PFS is different to the company analysis where survival has been estimated using patient-level data. In the case of OS and (to a lesser extent PFS) the EAG model underpredicts survival and using patient-level data for the COVID-unmodified survival reduces the EAG base case ICER compared with digitised curves.

EAG Response:

The EAG acknowledges that analyses were conducted using digitised Kaplan-Meier data to estimate pseudo-IPD because IPD were not made available to the EAG. This approach is consistent with standard practice in HTA when IPD is not provided by the company.

The EAG can confirm that the accuracy of the EAG’s digitised data produces is extremely high and are not the source of the difference between the EAG and company models. The observed differences noted by the company arise from the company’s implementation of background mortality, which applies a relative survival approach (adding background mortality to trial mortality). Whilst this was described in the company submission when describing background mortality, the CS also reported that standard parametric models were used, which led to this confusion.

The EAG notes the company’s view that the survival estimated from the EAG’s extrapolation has slightly lower survival probabilities compared with IPD (table 1: Company FAC check v3). This is consistent with the application of excess

background mortality to the EAG's extrapolations. The company has provided the parameters to survival models which account for background mortality, fitted to the COVID-unmodified data, which are used in the amended analyses presented later in this addendum, resolving this issue.

1.2 *Disparity in use of COVID-unmodified TTD*

Company:

The EAG uses the COVID-modified TTD curve and appear not to have attempted to produce their own COVID-unmodified TTD as done for OS and PFS, creating an inconsistency in the modelling of outcomes.

EAG Response:

TTD is a secondary outcome, capped at three years in the model, and therefore has limited impact on cost-effectiveness results. The EAG considered the company's chosen log-normal extrapolation to be reasonable and judged that further exploration of COVID-unmodified TTD would not materially affect decision uncertainty. The EAG were not provided with the COVID-unmodified TTD Kaplan-Meier plot, and so it was not possible for the EAG to use this data. Given that the company had implemented updated OS models in their additional comments, the EAG understands the company could also have updated TTD if they considered this a major issue. The EAG is happy for the company to implement the option for extrapolations of this data to be utilised within the economic model, but anticipates the impact to be small. The EAG also notes an inconsistency in the company's modelling of TTD for HMRN. The company's approach to modelling TTD uses HMRN data, whereas PFS and OS apply hazard ratios to extrapolations of EPCORE NHL-1 data, and are therefore not based on the same population.

1.3 *Impact on EAG's base case cost-effectiveness results*

Company:

The ICER for the EAG's base case reduces from [REDACTED] to [REDACTED] when IPD are used for the COVID-unmodified survival data. An updated table for the EAG's preferred assumptions is shown below in Table 1.

Table 1. EAG Preferred base case assumptions

Epcoritamab:	Corrected EAG analyses				
	Incremental costs	Incremental QALYs (no QALY weighing)	ICER (£/QALY)		
			Severity modifier	No severity modifier	% change in ICER vs Company base case
Company-corrected base case	[REDACTED]	3.328	[REDACTED]	*****	
EAG 01: Log-normal extrapolations for PFS and OS for epcoritamab based on <i>COVID-unmodified data</i> from EPCORE NHL -1 (Corrected EAG analysis uses parameters derived from PLD including the correct COVID-unmodified data for OS/PFS/TTD)	[REDACTED]	2.292	[REDACTED]	*****	[REDACTED]
Current 4L+ Care:					
EAG 02: Log-normal extrapolations for both PFS and OS for current 4L+ care using HMRN data directly (COVID-modified PLD used for epcoritamab for OS/PFS/TTD)	[REDACTED]	2.742	[REDACTED]	*****	[REDACTED]
Cumulative impact of EAG 01 – EAG 02 (Naïve analysis, COVID-unmodified data used for epcoritamab; log-normal for OS, PFS and TTD curves. As with EAG-01, the corrected EAG analysis uses PLD and the correct TTD (COVID-unmodified))	[REDACTED]	1.691	[REDACTED]	*****	[REDACTED]

Epcoritamab:	Corrected EAG analyses				
	Incremental costs	Incremental QALYs (no QALY weighing)	ICER (£/QALY)		
			Severity modifier	No severity modifier	% change in ICER vs Company base case
Company-corrected base case	████	3.328	████	*****	
EAG 03: Higher frequency of haematologist consultant visits in the first month in epcoritamab arm	████	3.328	████	*****	██
EAG 04: Utilities for PFS from EPCORE NHL-1 trial, adjusted for PD using wild et al	████	3.439	████	*****	██
EAG 05: Adverse events incidence in comparator arm based on reweighted data for R-CHOP (RELEVANCE), O-Benda (GADOLIN) and R ² (MAGNIFY) as reported in TA894	████	3.328	████	*****	██
EAG 06: Inclusion of grade 2 CRS events requiring treatment with tocilizumab	████	3.328	████	*****	██
Cumulative impact of all changes (EAG01 – EAG06)	████	1.712	**	████	████

Note: For analyses where the threshold for the severity modifier is met, the 'no severity modifier' ICER is greyed out; N/A – the threshold for severity modifier was not met for analysis therefore no severity-adjusted data reported.

EAG Response: The EAG accepts the revised analysis based on IPD but reiterates that the differences in outcomes were a result of the company's application of background mortality to survival data and not the digitisation of data. The EAG reports the deterministic and probabilistic cost-effectiveness results for the EAG's revised base case (which is similar to company's corrected analyses) in Table 2 and Table 4 below.

Table 2. Deterministic EAG base cost-effectiveness results with epcoritamab PAS discount

	Total Costs (£)	Total LYG	Total QALYs	Incremental Costs of Epcoritamab (£)	Incremental LYG of Epcoritamab	Incremental QALYs of Epcoritamab	ICER (£/QALYs)
Epcoritamab	████████	6.310	3.412				
Current 4L+Care	████████	2.798	1.700	████████	3.512	1.712	████████

*Analysis does not include severity modifier

A summary of net health benefits, at £30,000 threshold is shown in Table 3 below.

Table 3. Net benefit results in the EAG's base case analysis

Net monetary benefit (NMB) at £30,000	Net health benefit (NHB) at £30,000
████████	████████

Table 4 shows the probabilistic cost-effectiveness results for the EAG's revised base case. The resulting ICER is similar to the deterministic base case ICER.

Table 4. Probabilistic cost-effectiveness results, EAG base case with epcoritamab PAS discount

	Mean Total Costs (£)	Mean Total QALYs	Incremental Costs of Epcoritamab (£)	Incremental QALYs of Epcoritamab	ICER (£/QALYs)
Epcoritamab	████████	3.494			
Current 4L+Care	████████	1.744	████████	1.750	████████

The probability of epcoritamab being cost-effective at £30,000 threshold is █. The EAG's cost-effectiveness scatterplots is presented in Figure 1 and cost-effectiveness acceptability curve in Figure 2.



Figure 1. Incremental cost-effectiveness scatterplot of epcoritamab versus current 4L+ care, revised EAG base case

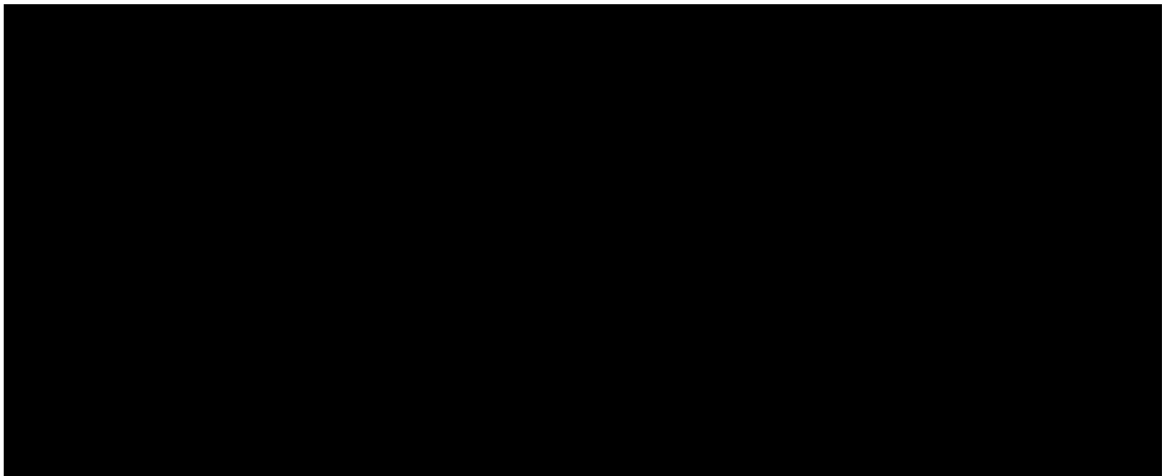


Figure 2. Cost-effectiveness acceptability curve of epcoritamab versus current 4L+ care

EAG exploratory analyses

Table 5 summarises the EAG’s deterministic cost-effectiveness results for the exploratory analyses (including those selected for the base case). The table also shows the impact on the company’s ICER of individual changes to the company’s base case. Table 6 shows additional scenario analyses (not reported in final EAG report) conducted using the EAG’s revised base case testing the impact of individual model assumptions on EAG’s base case ICER. Most of the scenarios revert to company’s preferred model assumptions.

Table 5. EAG exploratory analyses - epcoritamab vs current 4L+ care

Parameter varied	Base case value	Scenario value	Rationale	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Change in ICER (from company base case)
Corrected company base case					██████	3.994	██████	
Epcoritamab OS extrapolation	Lognormal	Exponential	The most pessimistic as it has the lowest goodness-of-fit statistics and produced the most pessimistic extrapolation of the models fitted to the data	Epcoritamab: 4.130 Current 4L+: 1.106	██████	3.023	██████	██████████)
MAIC hazard ratios	MAIC hazard ratios on unadjusted epcoritamab extrapolation	MAIC hazard ratios on extrapolations of HMRN data	To evaluate the impact of a different approach in assessing the efficacy of epcoritamab	Epcoritamab: 6.336 Current 4L+: 1.890	██████	4.445	██████	██████████)
Log-normal extrapolations for PFS and OS for epcoritamab.	Log-normal extrapolations for PFS and OS for epcoritamab based on Covid adjusted data from EPCORE NHL -1	Log-normal extrapolations for PFS and OS for epcoritamab based on COVID unadjusted data from EPCORE NHL -1	To assess the impact of using COVID unmodified epcoritamab data on cost-effectiveness results.	Epcoritamab: 3.915 Current 4L+: 1.165	██████	2.750	██████	██████████)

Parameter varied	Base case value	Scenario value	Rationale	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Change in ICER (from company base case)
Corrected company base case					■	3.994	■	
Survival extrapolations for current 4L+ care	MAIC HR used on adjusted epcoritamab data from EPCORE NHL-1 to get PFS and OS extrapolations for current 4L+ care.	Log-normal extrapolations for both PFS and OS for current 4L+ care using HMRN data directly	To evaluate the impact of using a different approach to get the survival outcomes for the current 4L+ care.	Epcoritamab: 5.176 Current 4L+: 1.885	■	3.291	■	■
Resource use (Haematologist consultant visit)	Once a month	Once weekly (cycle 0-4), then once monthly	To evaluate the impact of haematologist consultation visits based on EAG clinical expert advice.	Epcoritamab: 5.176 Current 4L+: 1.182	■	3.994	■	■)
Resource use (PET scans)	Not included	Once in a year	To explore the impact of the addition of PET scans to the resource use in PFS based on EAG clinical expert advice.	Epcoritamab: 5.176 Current 4L+: 1.182	■	3.994	■	■)

Parameter varied	Base case value	Scenario value	Rationale	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Change in ICER (from company base case)
Corrected company base case					██████	3.994	██████	
Adverse Events proportions in the current 4L+	AEs recorded for R-CHOP in TA892	Weighted proportions based on AEs for O-benda, R-CHOP and R2	To Evaluate the AEs in the current 4L+ based on AEs that represent the varying proportions of AEs across the therapies in the basket of care.	Epcoritamab: 5.176 Current 4L+: 1.182	██████	3.994	██████	██████
Grade 2 CRS AE occurring in > 5% in epcoritamab arm.	CRS = 0.00%	CRS = 12%	To assess the impact of including CRS AE in the epcoritamab arm	Epcoritamab: 5.176 Current 4L+: 1.182	██████	3.994	██████	██████
Utility for PFS and PD state.	Epcoritamab PFS: █████ Current 4L+ PFS: █████ PD: █████	PFS utility arms =0.800 PD =0.613	To explore the impact of using the same health state utility for both arms.	Epcoritamab: 5.414 Current 4L+: 1.287	██████	4.127	██████	██████
AE disutility	No AE disutility included	AE disutility included	To assess the AE disutility on QALYs	Epcoritamab: 5.169 1.176	██████	3.993	██████	██████

*Change in ICER based on company's base case (corrected for LDH cost). For all individual scenario analyses, the x1.2 severity modifier threshold was met – QALYs and ICERs reported are severity modified.

Table 6. Additional exploratory analyses on revised EAG base case, Epcoritamab PAS price applied

Scenario	Scenario values	Incremental cost	Incremental QALY		ICER		Change in ICER (from EAG base case)
			Severity Modifier (x1.2)	No severity modifier	Severity modifier (x1.2)	No severity modifier	
EAG revised base case	-	██████	N/A	1.712	██████	██████	██████
COVID modified data	COVID modified data	██████	N/A	2.811	██████	██████	██████
Company MAIC	MAIC hazard ratios applied to the unadjusted epcoritamab EPCORE NHL-1 data	██████	2.826	2.355	██████	██████	██████
COVID modified data AND company MAIC	COVID modified data AND company MAIC	██████	4.127	3.439	██████	██████	██████
Resource use (Haematologist consultant visit)	Once a month	██████	N/A	1.712	██████	██████	██████
Resource use (PET scans)	Once a year	██████	N/A	1.712	██████	██████	██████
Adverse Events proportions in current 4L+	Anaemia =4.5%, Neutropenia =90.30%, Leukopenia =30.80%	██████	N/A	1.712	██████	██████	██████

No CRS AE	No CRS AE applied	██████	N/A	1.712	██████	██████	██████████
AE disutility	AE disutility applied	██████	N/A	1.708	██████	██████	██████████

N/A means the threshold for severity modifier was not met for that scenario. Therefore severity-modified results not applicable
The EAG base case results do not include a severity modifier therefore the absolute and percentage changes for the analyses that met the severity modifier are still calculated based on the relevant severity-unadjusted ICERs

2 Supplementary information

In the updated economic model, the company has included an option to use reweighted epcoritamab curves to explore an independent modelling approach to “avoid a naïve comparison with HMRN”.

The EAG stands by the naïve comparison for the base case. Reweighting to the HMRN still depends on the same fragility of the MAIC, including small ESS, differences in study design between RCT and real-world studies, and not being able to include known prognostic factors in MAIC.

The company’s MAIC counter-intuitively decreased the HR, increasing the advantage of epcoritamab over current 4L+ care, and reweighting will not fix that concern. The EAG’s base case keeps both arms COVID-unmodified and directly models HMRN outcomes from its own data, which is both transparent and reproducible.