17 July 2024
EMA/OD/0000157895
EMADOC-360526170-1953764
Committee for Orphan Medicinal Products

Orphan designation withdrawal assessment report

Tepkinly (epcoritamab)
Treatment of follicular lymphoma
EU/3/22/2634

Sponsor: AbbVie Deutschland GmbH & Co. KG

Note

Assessment report as adopted by the COMP with all information of a commercially confidential nature deleted.

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1. Product and administrative information

Product	
Designated active substance	Epcoritamab
Other names	Tepkinly, epcoritamab, Anti-CD3E x Anti-MS4A1 IgG1 monoclonal antibody Anti-(CD3 epsilon) and anti-(membrane-spanning 4-domains subfamily A member 1) IgG1 monoclonal antibody GEN3013
International Non-Proprietary Name	Epcoritamab
Tradename	Tepkinly
Orphan condition	Treatment of follicular lymphoma
Sponsor's details:	AbbVie Deutschland GmbH & Co. KG Knollstrasse 67061 Ludwigshafen Am Rhein Germany
Orphan medicinal product designation procedural history	
Sponsor/applicant	AbbVie Deutschland GmbH & Co. KG
COMP opinion	12 May 2022
EC decision	21 June 2022
EC registration number	EU/3/22/2634
Type II variation procedural history	
Rapporteur / Co-rapporteur	Peter Mol / Ingrid Wang
Applicant	Abbvie Deutschland GmbH & Co. KG
Application submission	07 November 2023
Procedure start	25 November 2023
Procedure number	EMA/H/C/005985/II/0001
Invented name	Tepkinly
Approved extension of therapeutic indication	Tepkinly as monotherapy is indicated for the treatment of adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy. Further information can be found in the European public assessment report (EPAR) on the Agency's website: www.ema.europa.eu/en/medicines/human/EPAR/Tepkinly
CHMP opinion	27 June 2024
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Maria Elisabeth Kalland / Frauke Naumann-Winter
Sponsor's report submission	27 November 2023
COMP discussion and adoption of list of questions	18-20 June 2024
Sponsor's removal request	17 July 2024

2. Grounds for the COMP opinion

The COMP opinion that was the basis for the initial orphan medicinal product in 2022 designation was based on the following grounds:

- the intention to treat the condition with the medicinal product containing epcoritamab was considered justified based on preliminary clinical data which showed that heavily pre-treated patients with relapsed/refractory follicular lymphoma achieved partial or complete responses;
- the condition is life-threatening and chronically debilitating due to lymphadenopathy, splenomegaly, bone marrow dysfunction, and the potential of transformation to aggressive lymphoma;
- the condition was estimated to be affecting approximately 4.9 in 10,000 persons in the European Union, at the time the application was made;
- In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing epcoritamab will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that showed partial and complete responses in a high proportion of heavily pre-treated relapsed/refractory patients with follicular lymphoma who have failed several lines of approved therapies. The Committee considered that this constitutes a clinically relevant advantage.

Thus, the requirement under Article 3(1)(b) of Regulation (EC) No 141/2000 on orphan medicinal products is fulfilled.

The COMP concludes that the requirements laid down in Article (3)(1) (a) and (b) of Regulation (EC) No 141/2000 on orphan medicinal products are cumulatively fulfilled. The COMP therefore recommends the designation of this medicinal product, containing epcoritamab as an orphan medicinal product for the orphan condition: treatment of follicular lymphoma.

3. Review of criteria for orphan designation at the time of type II variation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

Follicular lymphoma (FL) represents the second most common subtype of non-Hodgkin's lymphoma (NHL), and the most common indolent NHL (iNHL), and constitutes approximately 20% of all new cases of NHL in western countries (Swerdlow et al., 2017). It is a mature B-cell lymphoproliferative disorder of transformed germinal center B-cells, consisting of a mixture of centrocytes (small to medium-sized cleaved follicular center cells) and centroblasts (large non-cleaved follicular center cells), that typically involves a follicular growth pattern for most of the cases (85%) (Alaggio et al., 2022; Smith et al., 2013; Xerri et al., 2016). This subtype of FL is now termed classic FL (cFL) and harbour the t(14;18)(q32;q21) translocation associated with IGH::BCL2 fusion and overexpression of

cytoplasmic B-cell leukaemia/lymphoma 2 (BCL2) protein. This type is separated from two related subtypes, specifically follicular large B-cell lymphoma (FLBL) and FL with uncommon features (uFL) (Alaggio et al., 2022).

FL includes a high degree of mutational and clinical heterogeneity, ranging from an indolent to a highly aggressive clinical course with a frequent need for several lines of treatment (Qualls et al., 2022). The World Health Organization (WHO) classification has earlier adopted a grading from 1-3, where grade 3 has been subdivided into grade 3a, in which centrocytes are present, and grade 3b, in which there are sheets of centroblasts (Ott et al., 2002). The clinical aggressiveness of FL increases with increasing numbers of centroblasts, and subsequently grades. FL grade 1-3a comprises the most prevalent indolent (low-grade) lymphoma subtype of NHL. In contrast, FL grade 3b, which largely equals to the recently defined subtype of FLBL, is at an intermediate stage of large cell transformation and is typically treated as an aggressive (high-grade) lymphoma (Alaggio et al., 2022; Dreyling et al., 2021; Swerdlow et al., 2017). The grading of FL, which is only pertinent to cFL, is no longer mandatory according to the latest revision of the WHO classification (Alaggio et al., 2022).

The aetiology of FL is still poorly understood. It has been suggested that age, gender, and ethnicity may affect a person's likelihood of developing FL. The incidence increases with age; although in principle FL may occur at any age, it is extremely rare in children and adolescents. The median age at diagnosis of FL is around 60-65 years. Although onset can be gradual at the time of initial diagnosis, advanced FL is typically incurable, and the response rates are lower with shorter durations of response with successive lines of therapy (Jacobsen, 2022).

The approved extension of the therapeutic indication "*Tepkinly as monotherapy is indicated for the treatment of adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy*" falls within the scope of the designated orphan condition "treatment of follicular lymphoma".

Intention to diagnose, prevent or treat

The medical plausibility is confirmed by the positive benefit/risk assessment of the CHMP, see EPAR.

Chronically debilitating and/or life-threatening nature

Patients with FL generally present with asymptomatic lymphadenopathy, with waxing and waning symptoms present for years. Most patients therefore have widespread disease at diagnosis, including peripheral and central (abdominal and thoracic) lymphadenopathy and splenomegaly. Approximately 10% of the patients have localized disease at diagnosis and less than 20% present with B symptoms (fever, night sweats and weight loss) and elevated serum lactate dehydrogenase (LDH) levels. The bone marrow is involved in around 40-70% of the cases, whereas involvement of other normal organs in extra-nodal sites is uncommon (Swerdlow et al., 2017; Freedman, 2020). Signs related to bone marrow involvement such as anaemia, leukopenia, or thrombocytopenia are rare at presentation but can be observed in the later stages of the disease.

Patients with advanced stage FL disease may experience B symptoms and suffer from unexplained fatigue/asthenia, local effects of lymphadenopathy such as abdominal pain, chest pain, cough or dyspnoea, or symptoms of bone marrow failure leading to cytopenia. Other symptoms depend on the location of the lymphoma (e.g., gastrointestinal bleeding due to gastrointestinal lymphomas, superior vena cava syndrome due to vein compression, renal failure due to ureter compression, and rarely spinal cord compression). Particularly patients with relapsed disease may have reduced quality of life.

The sponsor discussed the life-threatening nature of the disease. It is estimated that approximately 20% of patients experience disease progression within 24 months (POD24) of front-line therapy, which is a well-known predictor of a poor prognosis (Casulo et al., 2022), and that the 5-year overall survival (OS) rate is markedly lower in these patients compared to those without early progression (34-50% vs. 90%, respectively) (Casulo et al., 2016). Although life expectancy has improved due to recent therapeutic advances, FL patients frequently relapse and become progressively more refractory to subsequent lines of therapy. Advanced-stage FL is considered incurable with conventional chemotherapy, although patients often have good responses to treatment and might live for several years. The survival outcome worsens significantly as the patients progress through multiple lines of therapy and most patients eventually die of progressive lymphoma and its complications (Link et al., 2019). Moreover, histologic transformation to high-grade NHLs that are clinically more aggressive with a poor outcome is relatively common in FL patients, occurring at a rate of approximately 2-3% per year (Kridel et al., 2016; Freedman, 2018).

The sponsor has not identified any significant changes in the severe nature of the condition since the orphan designation in 2022. FL remains life-threatening and chronically debilitating, mainly due to lymphadenopathy, splenomegaly, bone marrow dysfunction, and the potential of transformation into aggressive lymphoma.

Number of people affected or at risk

At the time of the orphan designation in 2022, the COMP concluded that the condition was estimated to be affecting approximately 4.9 in 10,000 persons in the European Union (EU).

The sponsor performed a comprehensive review of recently published studies on population-based prevalence or incidence of FL (including all grades 1–3b) in the European community (EU+3 European Economic Area [EEA] countries) and re-examined the methods used to estimate the prevalence at the time the orphan designation was granted in 2022. Published data from national, regional, and global population-based cancer registries and other relevant sources including the interactive web-based European Cancer Information System (ECIS; 2020) database, the International Agency for Research on Cancer's (IARC)'s Global Cancer Observatory (GCO, formerly GLOBOCAN; 2020), Haematological Malignancy Research Network (HMRN), Yorkshire region in the UK; 2007-2016), and the Surveillance, Epidemiology and End Results (SEER) program in US (representing around 48% of the US population; 2018) were searched. In addition, literature searches on Embase, PubMed, Ovid, and ASH publications (1980/2000 to present) were conducted. The Eurostat database (EC, 2023) was used as the source of the updated total population data.

Two different methods were applied to estimate the prevalence of FL in the 27 EU member states (EU27), plus Iceland, Liechtenstein, and Norway (EU+3). In the first method, the FL complete prevalence was indirectly estimated using the incidence and mean disease duration. This method was based on assumptions regarding the proportion of total NHL incident cases that were FL subtype and the median overall survival (mOS) among patients with FL, which can be considered as a surrogate for mean disease duration. For countries with data, the country-specific proportion of FL in incident NHL cases was multiplied by the country-specific NHL incidence rate to obtain the FL incidence rate. Overall, 75% of the total EU+3 population had country-specific data. For the remaining 25% of the population from countries without country-specific data, the weighted average proportion of FL in NHL from all studies (16.5%) was used to estimate FL incidence.

For the duration of the disease, the sponsor included a total of 7 studies in the final review, 3 of which were based on Nordic countries (Ji et al., 2009; Junlén et al., 2015; Wahlin et al., 2012), one each from the Netherlands (Krol et al., 2003), France (Dandoit et al., 2015), Slovenia (Južnič et al., 2015),

and one additional study that covered multiple countries in Europe (Conconi et al., 2015). Of the 7 identified studies, 5 explicitly reported the mOS for FL and 2 reported sufficient data where mOS could be calculated or inferred. The mOS for the 5 studies where this was reported ranged from 5.8 years based on a registry of Dutch patients diagnosed with FL between 1981–1989 (Krol et al., 2003; considered outdated) to 13 years based on a French registry of patients diagnosed from 1980–2009 (Dandoit et al., 2015). Among the two remaining studies, a mOS of approximately 15 years was calculated based on extrapolation from a more recent cohort of FL patients in the Swedish Lymphoma Registry diagnosed from 2008–2010 (Junlén et al., 2015). In view of the findings from the literature review conducted, the sponsor estimated that the upper range of survival for FL patients in the European population is between 13 to 15 years. This estimate is considered plausible also in view of the median age of diagnosis of FL between 60 to 65 years.

Based on the review of the epidemiological data sources found and the assumptions made, a complete prevalence of FL from method 1 was estimated to 4.3 to 4.9 per 10,000 people in the EU+3 countries in 2023.

In the second method, the 43-year limited duration prevalence of FL in the EU+3 was also estimated indirectly. Given that the median age of onset for FL is approximately 60 years (Szumera-Ciećkiewicz et al., 2020; Alonso-Álvarez et al., 2017), the sponsor considered a 43-year prevalence a quite good approximation of the complete prevalence for FL.

The starting point for calculating the 43-year limited duration prevalence for FL was the 5-year prevalence of NHL in the EU+3 as available by country from the IARC's GCO in 2020. To determine the 10-year prevalence of NHL, the 5-year NHL prevalence rates were multiplied by the ratio of 10-year to 5-year prevalence of NHL as reported by the HMRN database (1.65) for each of the EU+3 countries. The 10-year FL prevalence rates were then calculated by multiplying the proportion of FL cases among 10-year NHL prevalent cases reported by HMRN (i.e., 25.7%) to the 10-year NHL prevalence obtained from the IARC's GCO in the first step for each of the EU+3 countries. Given the indolent nature of FL and its relative better survival as compared to other more aggressive NHL subtypes such as diffuse large B-cell lymphoma (DLBCL), the proportion of FL subtype among prevalent NHL cases was higher than that used in the first method, which was derived from incident cases. The 43-year FL prevalence rate was subsequently calculated by multiplying the ratio of 43-year/10-year FL prevalence from the SEER database (1.8) to the 10-year FL prevalence estimated in the second step for each of the EU+3 countries. This rate was then multiplied by the corresponding country-specific population size from Eurostat as of 01-Jan-2023 for each country to calculate the 43-year number of prevalent FL cases for each of the EU+3 countries. Finally, the 43-year prevalence rate of FL for the overall EU+3 countries was calculated by dividing the sum of all FL patients by the sum of the total population from all EU+3 countries. Based on the second method, the sponsor concluded on a 43-year limited duration prevalence estimate for FL of 4.8 per 10,000 people in the European community.

The upper range of the proposed prevalence estimates for FL using the first methodology, which was based on a disease duration of 15 years, as well as the estimate from the second method were largely in line with the rates reported at the time of the orphan designation for epcoritamab and is consistent with recent considerations accepted in orphan designations and for maintenances of the status that have been granted for FL from 2021 to 2023. The same conclusion as for the orphan designation can therefore be accepted for this procedure, that FL affects approximately 4.9 in 10,000 people in the EU.

Article 3(1)(b) of Regulation (EC) No 141/2000

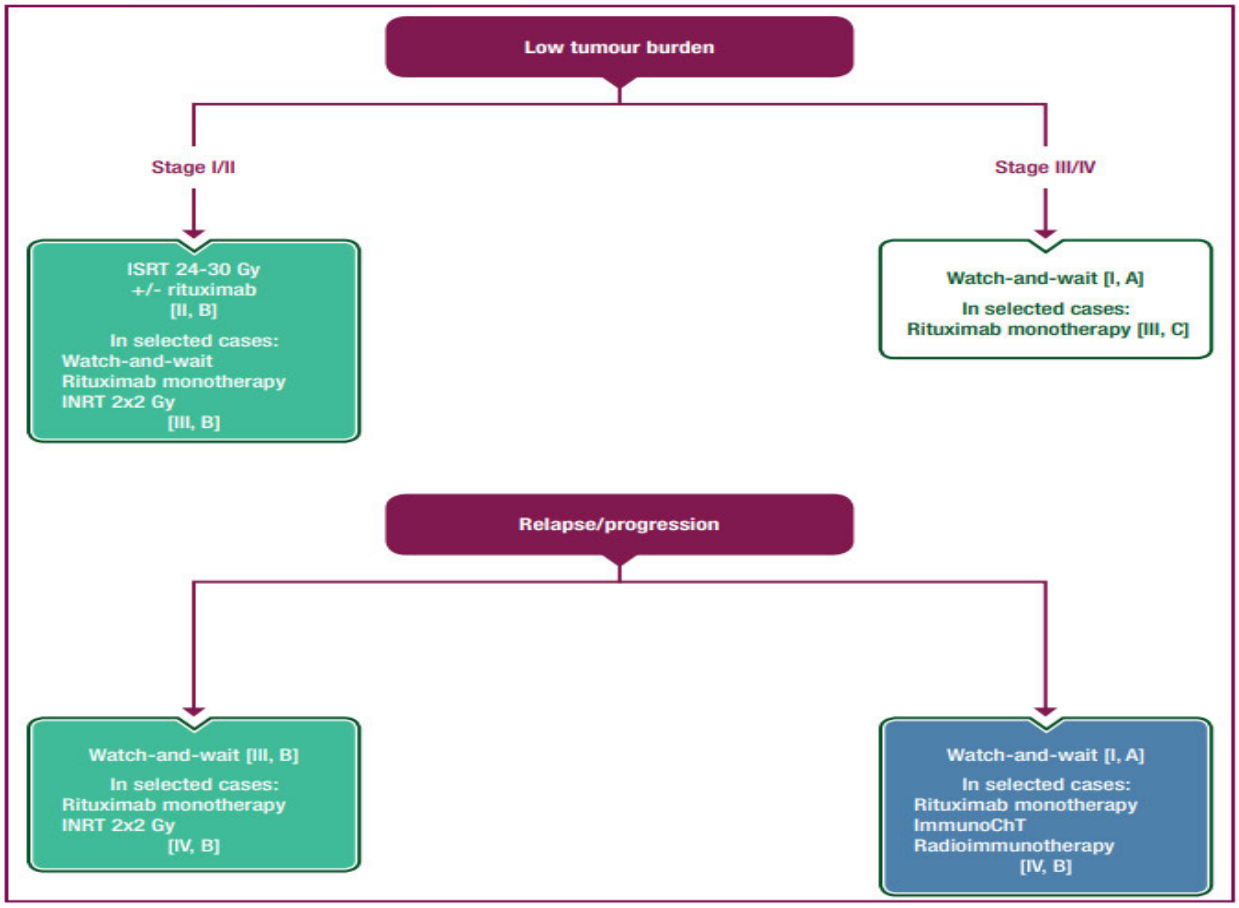
Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

The sponsor provided a list of medicinal products approved in the EU for the treatment of patients with r/r FL and their approved therapeutic indications. Several therapies are authorised both centrally and nationally in the EU for the treatment of adult patients with FL, NHL, and lymphomas. These medicines include rituximab (MabThera), obinutuzumab (Gazyvaro), lenalidomide (Revlimid), idelalisib (Zydelig), duvelisib (Copiktra), tisagenlecleucel (hereinafter referred to as tisa-cel, Kymriah), mosunetuzumab (Lunsumio), zanubrutinib (Brukinsa), axicabtagene ciloleucel (hereinafter referred to as axi-cel-cel, Yescarta), lisocabtagene maraleucel (hereinafter referred to as liso-cel, Breyanzi), pixantrone (Pixuvri), bendamustine chlorambucil, cyclophosphamide, doxorubicin, mitoxantrone, etoposide, prednisolone, and vincristine. Other treatment options also exist, such as radiotherapy, autologous- (ASCT) and allogenic stem cell transplantation (alloSCT).

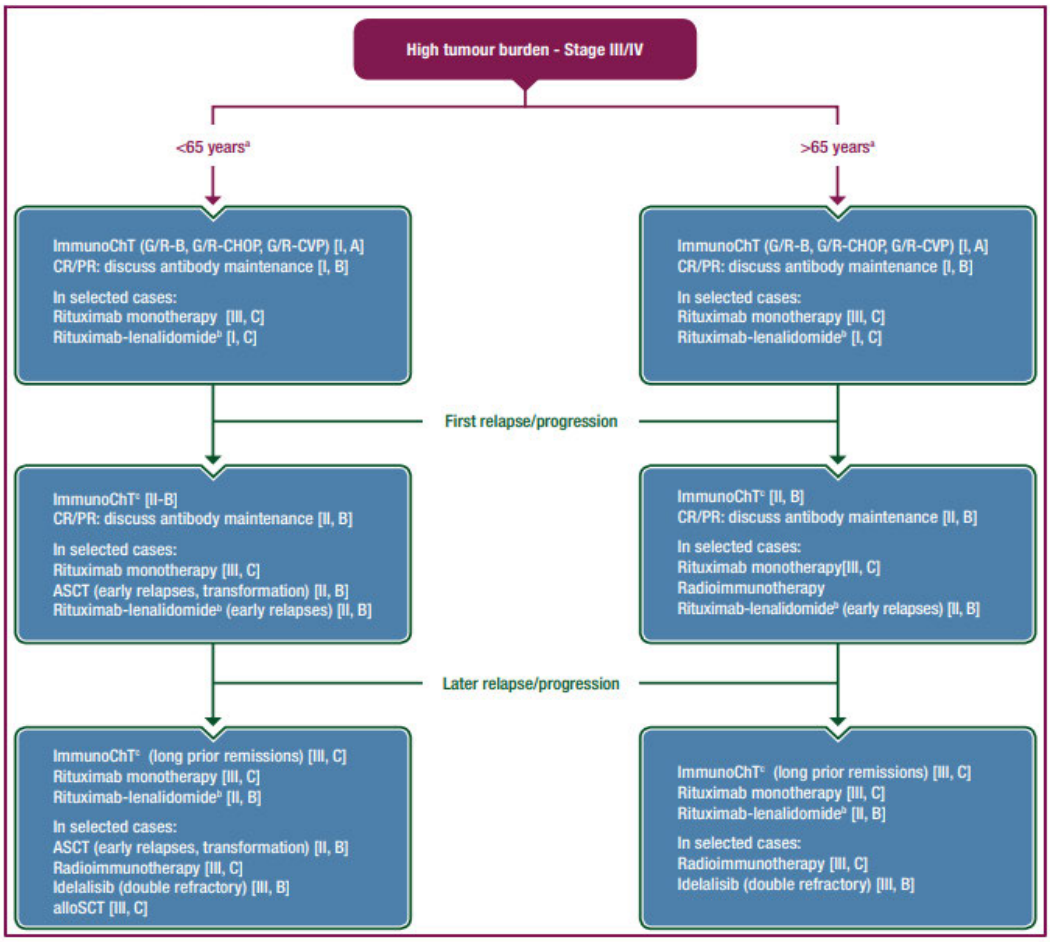
Patients with newly diagnosed FL are generally treated with an anti-CD20 antibody in monotherapy, rituximab (R) or obinutuzumab (G), or an anti-CD20-containing regimen (e.g., G/R-B, G/R-CHOP, and G/R-CVP). Available treatment options for r/r FL patients depends on the patient's health, age, stage of disease, the grade of FL, prior anti-lymphoma therapy, and the duration of response to prior therapy. The most recent ESMO guidelines for newly diagnosed and relapsed FL describe part of the current standard of care for these patients (Dreyling et al., 2021), expect for the medicines approved after its publication in 2021. According to the guidelines, therapy should be initiated only upon development of symptoms. The clinical treatment guidelines identify two types of FL populations that are offered two different treatment algorithms depending on their tumour burden, being either low (Figure 1) or high (Figure 2).

Figure 1. Treatment algorithm for FL patients with low tumour burden



cht, chemotherapy; fl, follicular lymphoma; inrt, involved-node radiotherapy; isrt, involved-site radiotherapy.

Figure 2. Treatment algorithm for FL patients with high tumour burden



allosct, allogeneic stem cell transplantation; asct, autologous stem cell transplantation; b, bendamustine; chop, cyclophosphamide, doxorubicin, vincristine, prednisolone; cht, chemotherapy; cr, complete response; cvp, cyclophosphamide, vincristine, prednisolone; fl, follicular lymphoma; g, obinutuzumab; pr, partial response; r, rituximab. a biological age (years). b off-label. c preferred in rituximab-refractory cases.

Tepkinly (epcoritamab) was granted a conditional MA in the EU (Product No. EMEA/H/C/005985) on 22-Sep-2023 for the treatment of adult patients with r/r DLBCL after two or more lines of systemic therapy. This indication extension of epcoritamab is intended to include treatment of adult patients with r/r FL who have received at least two prior lines of systemic therapy. An overview of medicinal products authorised for treatment of relapsed FL in the EU and whether they are considered satisfactory methods of treatment relevant for a discussion on the significant benefit of epcoritamab in FL is presented in the table below.

In summary, the therapeutic indications for tisa-cel (Kymriah), mosunetuzumab (Lunsumio), and zanubrutinib (Brukinsa) are covering the indication extension proposed for epcoritamab and are therefore considered to be satisfactory methods relevant for a discussion on the significant benefit of epcoritamab in the target FL population. The other medicinal products have more restricted indications as compared to that applied for epcoritamab and will not be further discussed in the significant benefit section below.

Table 1. Medicinal products authorised for the treatment of r/r FL in the EU

Product (INN)	**Procedure #, Approval Date, and Type of MA**	**Mechanism of Action (MoA)**	**Therapeutic indication per SmPC**	**Considerations regarding being a satisfactory method**
Zevalin ([90Y]-ibritumomab tiuxetan)	EMEA/H/C/000547 16 Jan 2004 Full MA	CD20 monoclonal antibody with radioisotopes	[90Y]-radiolabelled Zevalin is indicated as consolidation therapy after remission induction in previously untreated patients with FL [90Y]-radiolabelled Zevalin is indicated for the treatment of adult patients with rituximab relapsed or refractory CD20+ follicular B-NHL	Since Zevalin marketing authorization has been expired is not relevant to be discussed as satisfactory method
Zydelig (idelalisib)	EMEA/H/C/003843 18 Sep 2014 Full MA	PI3K inhibitor	Zydelig is indicated as monotherapy for the treatment of adult patients with FL that is refractory to two prior lines of treatment	Not a satisfactory method; covers only r/r FL patients who are refractory to at least two prior systemic therapies
Gazyvaro (obinutuzumab) plus bendamustine	EMEA/H/C/002799 13 Jun 2016 Full MA	CD20 antibody + bendamustine	Gazyvaro in combination with bendamustine followed by Gazyvaro maintenance is indicated for the treatment of patients with FL who did not respond or who progressed during or up to 6 months after treatment with rituximab or a rituximab-containing regimen	Not a satisfactory method; only indicated for patients with rituximab-refractory FL
Revlimid (lenalidomide) plus rituximab	EMEA/H/C/000717 18 Dec 2019 Full MA	CD20 antibody + lenalidomide	Revlimid in combination with rituximab (anti-CD20 antibody) is indicated for the treatment of adult patients with previously treated FL (Grade 1 – 3a)	Not a satisfactory method; only indicated for patients with r/r FL grade 1-3a*

Copiktra (duvelisib)	**EMEA/H/C/005381 19 May 2021 Full MA**	**PI3K inhibitor**	**Copiktra monotherapy is indicated for the treatment of adult patients with FL that is refractory to at least two prior systemic therapies**	**Not a satisfactory method; covers only r/r FL patients who are refractory to at least two prior systemic therapies**
Kymriah (tisagenlecleucel)	EMEA/H/C/004090 29 Apr 2022 Full MA	Anti-CD19 CAR-T	Kymriah is indicated for the treatment of adult patients with r/r FL after two or more lines of systemic therapy	Satisfactory method; complete overlap with the proposed extension of indication for epcoritamab
Lunsumio (mosunetuzumab)	EMEA/H/C/005680 03 Jun 2022 CMA	CD20xCD3 bispecific antibody	Lunsumio as monotherapy is indicated for the treatment of adult patients with r/r FL who have received at least two prior systemic therapies	Satisfactory method; complete overlap with the proposed extension of indication for epcoritamab
Yescarta (axicabtagene ciloleucel)	EMEA/H/C/004480 21 Jun 2022 Full MA	Anti-CD19 CAR-T	Yescarta is indicated for the treatment of adult patients with r/r FL after three or more lines of systemic therapy	Not a satisfactory method; covers only FL patients who have failed three or more lines of systemic therapy
Brukinsa (zanubrutinib) plus obinutuzumab	EMEA/H/C/004978 22 Nov 2021 Full MAA	BTK inhibitor	Brukinsa in combination with obinutuzumab is indicated for the treatment of adult patients with r/r FL who have received at least two prior systemic therapies.	Satisfactory method; complete overlap with the proposed extension of indication for epcoritamab

Copiktra (duvelisib)	**EMEA/H/C/005381 19 May 2021 Full MA**	**PI3K inhibitor**	**Copiktra monotherapy is indicated for the treatment of adult patients with FL that is refractory to at least two prior systemic therapies**	**Not a satisfactory method; covers only r/r FL patients who are refractory to at least two prior systemic therapies**
Pixuvri (pixantrone)	EMEA/H/C/002055 10-May-2012 Full MA	Anthracycline	Pixuvri is indicated as monotherapy for the treatment of adult patients with multiple relapsed or refractory aggressive non-Hodgkin B-cell lymphomas. The benefit of pixantrone treatment has not been established in patients when used as fifth line or greater chemotherapy in patients who are refractory to last therapy	Not a satisfactory method; covers only patients with aggressive NHL such as DLBCL and only FL grade 3b and is not approved in fifth and later lines of therapy

MoA: Mode of action
CMA: Conditional marketing authorisation
MA: Marketing authorisation
*Since grade 3b FL biologically is more closely related to DLBCL than to the other forms of FL, these patients are often treated as an aggressive lymphoma such as DLBCL, for which Tepkinly is authorised. Tepkinly will be intended for FL without any grade-relevant restrictions, since an extrapolation of the positive B/R balance of Tepkinly observed in the studied FL grade 1-3a and DLBCL populations to patients with FL grade 3b can be considered acceptable. The label of Tepkinly is thus for all grades of FL.

Significant benefit

The sponsor did not seek protocol assistance from EMA to get any advice on a suitable approach for collecting the evidence needed to justify significant benefit of epcoritamab over existing methods of treatment for patients with r/r FL who have received at least two prior lines of systemic therapy. However, prior to the granting of the orphan designation, they received scientific advice on the clinical development plan for epcoritamab to support a conditional marketing authorisation in FL by a type II variation (Procedures No. EMEA/H/SA/4478/2/2020/III, EMA/SA/0000148598, EMA/SA/0000125855 and EMA/SA/0000095173).

Epcoritamab is a bispecific T-cell engager that recognizes the T-cell antigen CD3, as well as the B-cell antigen CD20, which is a proven target for the treatment of FL. The sponsor argued significant benefit of epcoritamab in monotherapy based on a clinically relevant advantage and a major contribution to patient care compared to the satisfactory methods for patients with r/r FL in the third- and later lines setting.

The claim of significant benefit is based on the results from study GCT3013-01, an ongoing, global, open-label, multi-cohort, multicentre, single-arm phase 1/2 study that evaluate epcoritamab as monotherapy in patients (≥18 years) with r/r FL after two or more lines of systemic therapy. The study includes a dose escalation part, an expansion part and a 3-step step-up dose (SUD) optimisation part. Patients included in the study were required to have documented CD20+ mature B-cell neoplasm according to WHO classification 2016 or WHO classification 2008 based on representative pathology report with histologic confirmed FL grade 1-3a at initial diagnosis without clinical or pathological evidence of transformation. The pivotal iNHL expansion part of study GCT3013-01 (N=155) assessed the efficacy of epcoritamab monotherapy in 128 patients with r/r FL (01 FL cohort). The iNHL cohort also included 27 patients with other iNHL histologies/ subtypes (i.e., MZL and SLL). The data cut-off (DCO) date for the efficacy and safety analyses provided was 21-Apr-2023. At the DCO, the median duration of study follow-up was 17.4 months (range: 0.2, 30.1), whereas the median number of epcoritamab cycles initiated in the study was 8 (range: 1, 33).

The primary efficacy objective of the expansion part of study GCT3013-01 is to evaluate the antitumor activity of epcoritamab as a single agent in patients with mature B-cell lymphoma, including FL, as assessed by an independent review committee (IRC) using the Lugano classification criteria (Cheson et al., 2014). The primary efficacy endpoint ORR is defined as the best overall response (BOR) of a partial response (PR) or complete response (CR). Secondary efficacy endpoints included duration of response (DOR), CR rate (CRR), duration of complete response (DOCR), time to response (TTR), rate of minimal residual disease (MRD) negativity in patients who are in remission, progression-free survival (PFS), and OS.

The median number of prior lines of anti-lymphoma therapy in the FL cohort was 3 (range: 2-9). A total of 63.3% (81/128) of the patients had received at least 3 prior lines of systemic therapy. All patients had received prior alkylating-containing agents and anti-CD20 therapy, 77.3% (99/128) had received prior anthracycline therapy, and 31.3% (40/128) prior lenalidomide. Around two thirds of the enrolled patients (70.3%; 90/128) were double refractory to an anti-CD20 and alkylating agent, 52.3% (67/128) had POD24 after first line therapy, 78.9% (101/128) were refractory to prior anti-CD20 therapy, and 54.7% patients (70/128) were refractory to ≥ 2 consecutive lines of prior anti-lymphoma therapy. Only six of the patients (4.7%) had previously received CAR-T cell therapy before study entry, whereas 18.8% (24/128) had a prior ASCT, with 7.8% (10/128) relapsing within 12 months of ASCT.

Efficacy was evaluated in 128 patients who had received epcoritamab subcutaneously (SC) in cycles of 4 weeks, i.e., 28 days. The IRC-assessed ORR in r/r FL patients from the iNHL cohort was 82.0% (105/128; 95% confidence interval [CI]: 74.3, 88.3), where 62.5% (80/128; 95% CI: 53.5, 70.9) of the patients achieved a CR and 19.5% (25/128) obtained a PR. The median TTR to epcoritamab was 1.4 months and the median time to CR (TTCR) was 1.5 months in patients with FL. The responses were durable and the median DOR per IRC-assessment was not reached (95% CI: 13.7, not reached [NR]), with an estimated 68.7% remaining in response at 12 months. The median DOR among those who achieved a CR was not reached (95% CI: 21.4, NR), with an estimated 82.2% of them remaining in CR at 12 months. The median IRC-assessed PFS in patients with FL was 15.4 months (95% CI: 10.9, NR), while the median OS was not reached (95% CI: NR, NR). Of note, PFS and OS are time dependent endpoints that do not isolate the efficacy of the medicine in a single-arm study.

A comparison of efficacy (Table 2) and safety (Table 3) of epcoritamab versus the satisfactory methods is presented below:

Table 2. Comparison of efficacy of epcoritamab versus the satisfactory methods

Drug Name	**Epcoritamab**	**Tisa-cel**	**Mosu**
Approval Type	NA	Full	Conditional
MoA	Bispecific Ab	CAR T	Bispecific Ab
RoA	SC	IV	IV
Response evaluable set (N)	128	94	90
ORR %	82	86.2	80.0
CRR %	62.5	69.1	60.0
Median DOR (months)	NR	NR	22.8
Median PFS (months)	15.4	18.4	17.9

Ab = antibody; CAR T = chimeric antigen receptor T-cell therapy DOR = duration of response; FL = follicular lymphoma; IV = intravenous; IWG = international working group mosu = mosunetuzumab; NL = not listed; NR = not reached; ORR = overall response rate; OS Overall survival; PFS = progression-free survival; RoA = route of administration; SC = subcutaneous; tisa-cel = tisagenlecleucel.

Table 3. Comparison of safety of epcoritamab versus the satisfactory methods

Safety Overview, %	**Epcoritamab[a]**	**Tisa-cel[i]**	**Mosu[j]**
Analysis Population (n)	129	97	218
% AEs (related)	98.4 (93.0)	99 (78.4)	98.2 (86.2)
% AEs Grade ≥ 3 (related)	69.0 (37.2)	78.4 (46.4)	66.5 (NL)
% AEs leading to dose delayed (related)	59.7 (34.9)	NL	NL
% AEs leading to permanent discontinuation of study drug (related)	18.6 (3.9)	NL	4.1 (1.8)
% Serious AEs (related)	69.0 (46.5)	43.3 (29.9)	52.3 (34.4)
% Fatal AEs (no PD) (related)	10.1 (0)	7.2(NL)	1.8 (NL)

The sponsor also presented a comparison of adverse events for epcoritamab versus the satisfactory methods (Table 4).

Table 4. Comparison of adverse events for epcoritamab versus the satisfactory methods

Adverse Events, %	**Epcoritamab[a]**	**Tisa-cel[i]**	**Mosu[j]**
Sample size (n)	129	97	90
CRS (all Grade and [Grade ≥ 3][b])	46.7 (0)*	48.5 (0)	44.4 (2.2)
TLS (all Grade and [Grade ≥ 3])	0 (0)*	NL	NL
ICANS (all Grade and [Grade ≥ 3])	0 (0)*	4.1 (1)	NL
Neurologic events (all Grade and [Grade ≥ 3])	48.1 (2.3) 31.8 (2.3)†	37.1 (3.1)	56 (5)
Cytopenia (Grade ≥ 3 only):			
Febrile neutropenia	3.1	10.3	0
Neutropenia	17.1	32.0	27
Anaemia	6.2	13.4	8
Thrombocytopenia	3.9	9.3	4
Upper respiratory infections (all Grade and [Grade ≥ 3])	13.2 (0)	NL	NL
Pneumonia (all Grade and [Grade ≥ 3])	7.8 (5.4)	NL	NL
Rash (any Grade and [Grade ≥ 3])	8.5 [0]	NL	NL
Colitis (all Grade and [Grade ≥ 3])	0.8 (0)	NL	NL
Diarrhoea (all Grade and [Grade ≥ 3])	26.4 (1.6)	17.5 (1)	17 (0)
Nausea (all Grade and [Grade ≥ 3])	17.1 (0)	12.4 (2.1)	17 (0)
Vomiting (all Grade and [Grade ≥ 3])	8.5 (0)	7.2 (0)	NL
Pyrexia (all Grade and [Grade ≥ 3])	24.8 (2.3)	11.3 (1)	29 (1)
Fatigue (all Grade and [Grade ≥ 3])	30.2 (2.3)	15.5 (3.1)	37 (0)

A comparison of selected baseline characteristics of the patient populations enrolled in study GCT3013-01 for epcoritamab versus the pivotal clinical comparator studies for the satisfactory methods is presented below (Table 5).

Table 5. Comparison of background patient population for patients with FL enrolled in study GCT3013-01 (epcoritamab) versus the pivotal clinical comparator studies for the satisfactory methods

Drug Name	**Epcoritamab[a]**	**Tisa-cel[i]**	**Mosu[j]**
N	128	94	90
Median age (range)	66 (39-84)	57 (29-73)	60.0 (29-90)
Age ≥ 65 years, %	52.3	25.5	31.1
Prior lines of treatment			
1	0	0	0
2	36.7	25.5	37.8
≥ 3 (3, > 3)	63.3 (32.0, 31.3)	74.4 (20.2, 54.2)	62.2 (31.1, 31.1)
Median prior LOT (range)	3 (2-9)	4 (2-13)	3 (2-10)
Refractory to last LOT (%)	69	78.7	68.9
Double refractory to anti-CD20 and alkylating agent (%)	70	69.1	53.3
FLIPI 3-5 (%)	61	60.6	44.4
POD24	52.3	64.9	52.2

Significant benefit of epcoritamab versus tisa-cel (Kymriah)

The efficacy and safety of the CAR-T cell therapy tisa-cel in patients with r/r FL who had received two or more lines of systemic therapy were evaluated in the pivotal, global, multicentre, open-label, single-arm phase 2 study E2202 (also known as ELARA) (N= 98/97 ITT/mITT). The sponsor claimed significant benefit of epcoritamab versus tisa-cel based on improved efficacy in terms of clinically meaningful benefits in certain patient subgroups, improved safety, and major contribution to patient care.

According to the sponsor, epcoritamab showed comparable response rates to tisa-cel (ORR: 82% [95% CI: 74.3, 88.3] vs. 86.2% [95% CI: 77.5, 92.4] and CRR: 62.5% [95% CI: 53.5, 70.9]) vs. 69.1% [95% CI: 58.8, 87.3]), by direct treatment comparison (Table 3). However, the sponsor claimed that as summarised in Table 6 that patients with FL in ELARA were more heavily pretreated and a higher proportion had POD24, prior ASCT, and was refractory to last line of therapy. The sponsor also presented a comparison of efficacy in different subgroups (data not shown).

A more detailed characterization of the patient population vis a vis tisa-cel is provided on Table 6.

Table 6. Characterization of patient populations represented in study GCT3013-01 and ELARA

Baseline characteristics	GCT3013-01	GCT3013-01 subjects excluded from ELARA	GCT3013-01 subjects overlapping with ELARA	ELARA
Therapy	epcoritamab	epcoritamab	epcoritamab	tisa-cel
	N = 128	n = 38	n = 90	N = 97
ECOG 2	7 (5.5%)	7 (18.4%)	0 (0%)	0 (0%)
Lymphocyte count ≤0.3*10^9g/L	8 (6.25%)	8 (21.0%)	0 (0%)	0 (0%)
Hemoglobin <80g/L (i.e., ,8g/dL)	2 (1.6%)	2 (5.3%)	0 (0%)	0 (0%)
Moderate/ severely impaired renal, CrCl<60 ml/min	22 (17.2%)	22 (57.9%)	0 (0%)	0 (0%)
Baseline oxygen saturation ≤ 90%	1 (0.8%)	1 (2.6%)	0 (0%)	0 (0%)
Prior CAR T	6 (4.7%)	6 (15.8%)	0 (0%)	0 (0%)
Mean age (SD)	63.2 (11.2)	67.4 (11.3)	61.5 (10.7)	-
Median Age (range)	65 (39-84)	70 (43-84)	63 (39-83)	57 (IQR: 49-64)
Age ≥65, n (%)	67 (52.3%)	26 (68.4%)	41 (45.6%)	24 (24.7%)
<65 yrs	61 (47.7%)	12 (31.6%)	49 (54.4%)	73 (75.3%
≥75 yrs	17 (13.3%)	10 (26.3%)	7 (7.8%)	-
Male, n (%)	79 (61.7%)	21 (55.3%)	58 (64.4%)	64 (66.0%)
Prior LOTs, Median (range)	3 (2-9)	3 (2-9)	3 (2-9)	4 (2-13)
Prior LOTs≥3, n (%)	81 (63.3%)	28 (73.7%)	53 (58.9%)	74 (75.5%)
Prior LOTs≥4, n (%)	40 (31.3%)	17 (44.7%)	23 (25.6%)	
Prior LOTs≥5, n (%)	23 (18.0%)	12 (31.6%)	11 (12.2%)	27 (27.8%)-
POD24, n (%)	67 (52.3%)	20 (52.6%)	47 (52.2%)	61 (62.9%)*
Prior ASCT, n (%)	24 (18.8%)	4 (10.5%)	20 (22.2%)	35 (36.1%)
Double refractory, n (%)	90 (70.3%)	29 (76.3%)	61 (67.8%)	66 (68.0%)
Refractory to last prior LOT, n (%)	88 (68.8%)	25 (65.8%)	63 (70%)	76 (78.4%)
ECOG 0, n (%)	70 (54.7%)	17 (44.7%)	53 (58.9%)	56 (56.7%)
ECOG 1, n (%)	51 (39.8%)	14 (36.8%)	37 (41.1%)	41 (43.3%)
FLIPI: 0-1, n (%)	17 (13.3%)	5 (13.2%)	12 (13.3%)	39 (40)
FLIPI: 2, n (%)	31 (24.2%)	6 (15.8%)	25 (27.8%)	
FLIPI ≥3, n (%)	78 (60.9%)	26 (68.4%)	52 (57.8%)	58 (60%)
Ann Arbor Stage 1, n (%)	5 (3.9%)	2 (5.3%)	3 (3.3%)	14 (14.4%)
Ann Arbor Stage 2, n (%)	14 (10.9%)	4 (10.5%)	10 (11.1%)	
Ann Arbor Stage 3, n (%)	32 (25.0%)	11 (28.9%)	21 (23.3%)	83 (85.6%)
Ann Arbor Stage 4, n (%)	77 (60.2%)	21 (55.3%)	56 (62.2%)	

A MAIC analysis was conducted to compare the response rates (ORR and CRR), after adjusting the clinical characteristics and disease severity on the patient population of study GCT3013-01 that overlapped with that of ELARA based on the inclusion criteria (N=90). Following adjustments of key baseline demographics and clinical variables, including age, sex, ECOG PS, disease stage, FLIPI score, prior ASCT, POD24, refractoriness to last prior therapy and to previous anti-CD20 therapy, double refractory disease, elevated lactate dehydrogenase, and number of prior lines of therapy, an effective sample size (ESS) of 44 patients from study GCT3013-01 was compared to the 97 patients treated

with tisa-cel in ELARA. No adjustment was conducted based on bulky disease due to differences in the definitions applied across the studies.

The adjusted ORR and CRR were not significantly different between epcoritamab and tisa-cel (ORR 85.5% vs. 86.2%, odds ratio = 0.948 [95% CI: 0.321, 2.802], p = 0.923; CRR: 65.7% vs. 69.1%, odds ratio = 0.900 [95% CI: 0.419, 1.933], p = 0.785). At a median follow-up of 14.8 months, the median DOR and DOCR for epcoritamab in study GCT3013-01 was NR, with an estimated 68.7% and 81.1% of the FL patients remaining in response at 12 months, respectively. The median DOR and DOCR for tisa-cel was NR in ELARA (at a median follow-up of 28.9 months) (Dreyling et al, 2022).

The sponsor argued that because of the COVID-19 pandemic, the DOR to epcoritamab in the iNHL cohort of study GCT3013-01 was negatively affected, since it was conducted at the peak of the pandemic and when the highly infectious Omicron variants were prevalent globally. At a median follow-up of 14.8 months, the median DOR and DOCR for epcoritamab in study GCT3013-01 was NR, with an estimated 68.7% and 81.1% of patients remaining in response at 12 months, respectively. In contrast, ELARA was not conducted during the COVID-19 pandemic. The median DOR and DOCR for tisa-cel in ELARA was NR (at a median follow-up of 28.9 months). In a real-world evidence report, patients with FL who initiated any treatment during the COVID-19 pandemic were observed to have a nearly 4-fold increase in mortality risk compared to patients treated before the pandemic (Sehn et al., 2023). In addition, sensitivity analysis has shown that the COVID-19 associated deaths impacted the efficacy data of epcoritamab in the iNHL expansion part of study GCT3013-01, in particular the time-to-event analyses, that could possibly explain the shorter median DOR and PFS at the DCO.

The sponsor also claimed that epcoritamab provided clinically relevant advantage over tisa-cel based on improved safety. The overall safety profile showed a lower proportion of patients with grade ≥ 3 adverse events (AEs; including related) in study GCT3013-01 in comparison to those reported in ELARA (69% [37.2%] vs. 78% [46.4%]) (Table 3). Still, higher rates of serious AEs (including related) were observed with epcoritamab versus tisa-cel (69.0% [46.5%] vs. 43.3% [29.9%]). Similarly, the rate of fatal AEs was higher with epcoritamab (10.1 % vs. 7.2%). The sponsor argued that the higher rates of serious AEs and fatal AEs were mostly driven by COVID-19 infections. In the Safety Pool 01 for r/r FL (N=129), 25 patients (19.4%) experienced serious COVID-19 infections, with 6 patients (4.7%) having fatal outcomes. The incidence of COVID-19 and deaths due to COVID-19 in the expansion cohort of study GCT3013-01 were comparable to that seen in a retrospective study of patients with B-NHL who were treated with CD20 targeting T-cell engaging bispecific antibodies (30% of patients had a COVID-19 event and 21% died due to COVID-19) (Nachar et al., 2023). No fatal AE was considered related to epcoritamab.

According to the sponsor, comparison of individual AEs of special interest (AESIs) showed that epcoritamab had a more favourable safety profile compared to tisa-cel. Data from the FL optimization cohort with 3-step SUD regimen showed that the incidence and severity of cytokine release syndrome (CRS; all grade [grade ≥ 3]) in patients treated with epcoritamab was comparable to tisa-cel (46.7% [0] vs. 48.5% [0]). The registrational study conducted to support the approval of tisa-cel used ASTCT Lee 2014 grading criteria (Lee et al., 2014), which had different thresholds and criteria than the ASTCT Lee 2019 criteria used in study GCT3013-01 (Lee et al., 2019). As the threshold defining grade 3 CRS is lower with ASTCT Lee 2019, grade ≥ 3 CRS cases may be higher in the pivotal study for tisa-cel when applying the criteria based on ASTCT Lee 2019.

The incidence and severity of immune effector cell associated neurotoxicity syndromes (ICANS) and neurological toxicity in patients treated with epcoritamab compared favourably with the rates reported in ELARA with tisa-cel. From the FL Optimization Part with the 3-step SUD regimen, no ICANS event was observed with epcoritamab versus tisa-cel (all grade [grade ≥ 3]: 4.1% [1%]) (Table 4). From the

2-step SUD regimen, the neurotoxicity rates (any grade) were lower with epcoritamab (35.3% with Broad definition or 25.7% with Topp definition) compared to axi-cel (64%), and similar to tisa-cel (37.1%). Grade ≥ 3 neurological toxicities were numerically lower in epcoritamab (2.3% based on Broad definition or Topp definition) compared to tisa-cel (3.1%) (Table 5). Furthermore, from the 2-step SUD regimen, the rates of grade ≥ 3 cytopenia were lower in patients treated with epcoritamab compared to those treated with tisa-cel (3.1% vs. 10.3% febrile neutropenia, 17.1% vs. 32% neutropenia, 6.2% vs. 13.4% anaemia, and 3.9% vs. 9.3% thrombocytopenia, respectively) (Table 4).

Regarding the major contribution to patient care argument, the sponsor highlighted that SC administration of epcoritamab results in a shortened overall administration time. It also provides convenience for healthcare professionals and patients. These attributes may be particularly important for patients with indolent lymphoma. Tisa-cel is administered as IV infusion. In addition, the SC administration route results in a favourable pharmacokinetic profile, with a lower peak-to-trough ratio.

Patient satisfaction on the SC route of administration for epcoritamab monotherapy was assessed during a qualitative patient experience interview. Of the 20 patients from study GCT3013 01 study who participated in the interview, 4 patients (20%) were from the FL cohort and 16 patients (80%) were from the LBCL cohort. The participating patients were from France (55%), the UK (20%), and the US (25%). Seventy percent (14/20) of patients were interviewed after their Cycle 10 visit, and 30% (6/20) of patients had terminated early (either due to disease progression or unacceptable toxicity prior to Cycle 10). The proportion of males and females were equal, and the mean age of patients was 66 years (range: 21-84).

The majority of patients (17/20 [85%]) described the SC injections as a positive or neutral experience, and liked that the injection was short, did not hurt, and was minimally invasive or was practical (16/20 [80%]). Around two-thirds (11/19 [57.9%]) of the patients who provided response regarding treatment preference reported a preference to receiving treatment by injection under the skin over the IV mode of administration.

The sponsor also discussed the reduced staff time and increased institutional capacity (reduced chair time) for SC administration of epcoritamab to patients in the hospital setting as compared to IV administration of the CAR-T cell therapy axi-cel (Yescarta). An institutional resource analysis was developed to assess the practice efficiencies associated with SC administration of epcoritamab for patients with r/r FL after at least two lines of treatment. A total of 33 hours of personnel time were saved per treated patient, with comparable chair time. Although the analyses were conducted versus IV infusion of axi-cel, the sponsor argued that a similar analysis can be applied to other therapies that are administered IV, including tisa-cel (CAR-T cell therapy).

The sponsor further argued that epcoritamab is expected to introduce a major contribution to patient care over CAR-T cell therapies such as tisa-cel due to increased accessibility. In addition, their toxicity profiles may limit their use, as they require rigorous selection criteria, inpatient administration, and particular training and expertise, resulting in restricted availability and limitation of the treatments to tertiary care facilities. Epcoritamab provides the benefits of an off-the-shelf immunotherapy and can be used in all centres specialised in treating oncology patients without delay and without the limitations of individual manufacturing of CAR-T cell therapies, that may preclude access by patients with a rapidly progressing disease in urgent need for treatment.

COMP discussion

The data presented is considered insufficient to demonstrate an improved efficacy of epcoritamab over tisa-cel in FL. In comparison to tisa-cel, lower ORR and CRR were reported for epcoritamab (ORR: 82%

vs. 86.2% and CRR: 62.5% vs. 69.1%), by descriptive side-by-side treatment comparison (Table 3). The MAIC results did not show statistically significant differences between epcoritamab and tisa-cel. In addition, comparison of efficacy outcomes in different subgroups within or across studies is considered unreliable. This is even worsened by the single-arm design of the two pivotal studies and is therefore not discussed in further detail.

The claim of improved safety based on the frequencies of overlapping toxicities does not reflect the whole picture and biases due to differences in patient characteristic cannot be excluded. In addition, higher rates of serious AEs (including related) were reported for epcoritamab versus tisa-cel. Given the limited experience with epcoritamab from a small single-arm study with limited follow-up, the claim of improved safety in comparison to tisa-cel cannot be concluded on at present stage and no adequate quantification is possible for the descriptive cross-study comparison presented.

A significant limitation of the results from the patient experience interview is that they were conducted with patients from a single-arm study and hence there is no other treatment to compare the reported findings with. The results from these interviews can therefore not be considered as robust and decisive evidence of a major contribution to patient care. In addition, the argument for practice efficiency gain with epcoritamab is not considered to constitute a major contribution to patient care as it relates more to the treating professionals than to the patient itself.

The COMP acknowledged the sponsors' argument that treatment with epcoritamab provides the benefits of an off-the-shelf immunotherapy which can be used in all centres specialised in treating oncology patients without delay and without the limitations of individual manufacturing of CAR-T cell therapies, that may preclude access by patients with a rapidly progressing disease in urgent need for treatment. However, it should be recalled that a product's claim of major contribution to patient care cannot be established in the absence of the demonstration of the product's equivalence in terms of efficacy, safety, and benefit/risk balance with the relevant authorised medicinal products, i.e., in this case tisa-cel. Reference is made, in this respect, to the 2016 "Commission notice on the application of Articles 3, 5 and 7 of Regulation (EC) No 141/2000 on orphan medicinal products". Based on the data provided by the sponsor, a positive conclusion on the product's (epcoritamab) equivalence in terms of efficacy, safety, and benefit/risk balance versus tisa-cel (Kymriah), cannot be drawn. In turn, a claim of major contribution to patient care over tisa-cel cannot be established.

The sponsor should further discuss the arguments for significant benefit based on a clinically relevant advantage over tisa-cel for the target patient population and based on updated efficacy data from the iNHL cohort of study GCT3013-01 at the latest available DCO. Conductance of an efficacy analysis in a subset of patients with r/r FL who had progressed or relapsed after prior treatment with tisa-cel before entering study GCT3013-01, if anyone, could be used to demonstrate a clinically relevant advantage of epcoritamab in FL.

Significant benefit of epcoritamab versus mosunetuzumab (Lunsumio)

The efficacy and safety of the bispecific (CD3xCD20) antibody mosunetuzumab in adult patients with r/r FL after two or more lines of systemic therapy were evaluated in the pivotal, global, multicentre, open-label, dose-escalation and dose-expansion single-arm phase 1/2 study GO29781 (N=90). The sponsor claimed significant benefit of epcoritamab versus mosunetuzumab based on improved efficacy, improved safety and major contribution to patient care.

According to the sponsor, epcoritamab demonstrated clinically relevant advantage over mosunetuzumab, by providing therapeutic benefit across a broader spectrum of the target FL population and disease severity. Given the more stringent eligibility criteria, the therapeutic benefit of mosunetuzumab as demonstrated in GO29781 is only applicable to 63% of the patient population

represented in study GCT3013-01. Overall, study GCT3013-01 enrolled a higher proportion of elderly patients with heavily pretreated, highly refractory, and high-risk disease characteristics that is clinically very challenging to treat, representing a population with high unmet medical need (Table 7).

Table 7. Characterization of patient population represented in study GCT3013-01 and GO29781.

Baseline Characteristics	GCT3013-01	GCT3013-01 subjects excluded from GO29781	GCT3013-01 subjects overlapping with GO29781	GO29781 Budde et al. (2022)
Therapy	epcoritamab N = 128	epcoritamab n = 47	epcoritamab n = 81	mosunetuzumab N = 90
ECOG 2	7 (5.5%)	7 (14.9%)	0 (0%)	0 (0%)
Hemoglobin <100g/L (i.e., <10g/dL)	19 (14.8%)	19 (40.4%)	0 (0%)	0 (0%)
Moderate/ severely impaired renal function (CrCl <60 ml/min)	22 (17.2%)	22 (46.8%)	0 (0%)	0 (0%)
Ongoing bronchospasm or obstructive pulmonary disease	8 (6.3%)	8 (17.0%)	0 (%)	0 (0%)
Mean age (SD)	63.2 (11.2)	68.0 (10.29)	60.4 (10.81)	-
Median Age (range)	65 (39-84)	70 (43-84)	62 (39-83)	60 (IQR: 53–67)
Age ≥65, n (%)	67 (52.3%)	36 (76.6%)	31 (38.3%)	30 (33%)
<65 yrs	61 (47.7%)	11 (23.4%)	50 (61.7%)	60 (67%)
≥75 yrs	17 (13.3%)	12 (25.5%)	5 (6.2%)	-
Male, n (%)	79 (61.7%)	24 (51.1%)	55 (67.9%)	55 (61%)
Prior LOTs, Median (range)	3 (2-9)	3 (2-9)	3 (2-9)	3 (IQR 2-4)
Prior LOTs≥3, n (%)	81 (63.3%)	36 (76.6%)	45 (55.6%)	56 (62%)
Prior LOTs≥4, n (%)	40 (31.3%)	21 (44.7%)	19 (23.5%)	28 (31%)
Prior LOTs≥5, n (%)	23 (18.0%)	12 (25.5%)	11 (13.6%)	-
Progression with 24 months of 1st line (POD24), n (%)	67 (52.3%)	24 (51.1)	43 (53.1)	47 (52%)
Prior ASCT, n (%)	24 (18.8%)	8 (17.0%)	16 (19.8%)	19 (21%)
Double refractory (i.e., to anti-CD20 and alkylator, [DR]), n (%)	90 (70.3%)	33 (70.2%)	57 (70.4%)	48 (53%)
Refractory to last prior LOT, n (%)	88 (68.8%)	32 (68.1%)	56 (69.1%)	62 (69%)
ECOG 0, n (%)	70 (54.7%)	17 (36.2%)	53 (65.4%)	53 (59%)
ECOG 1, n (%)	51 (39.8%)	23 (48.9%)	28 (34.6%)	37 (41%)
FLIPI: 0-1, n (%)	17 (13.3%)	3 (6.4%)	14 (17.3%)	26 (29%)
FLIPI: 2, n (%)	31 (24.2%)	3 (6.4%)	28 (34.6%)	24 (27%)
FLIPI ≥3, n (%)	78 (60.9%)	40 (85.1%)	38 (46.9%)	40 (44%)
Ann Arbor Stage 1, n (%)	5 (3.9%)	2 (4.3%)	3 (3.7%)	5 (6%)
Ann Arbor Stage 2, n (%)	14 (10.9%)	5 (10.6%)	9 (11.1%)	16 (18%)
Ann Arbor Stage 3, n (%)	32 (25.0%)	9 (19.1%)	23 (28.4%)	25 (28%)
Ann Arbor Stage 4, n (%)	77 (60.2%)	31 (66.0%)	46 (56.8%)	44 (49%)

Efficacy analysis by descriptive side-by-side treatment comparison showed that the response rates (ORR and CRR) of epcoritamab were comparable to those of mosunetuzumab (ORR: 82% [95% CI: 74.3, 88.3] vs. 80.0% [95% CI: 70.3, 87.7] and CRR: 62.5% [95% CI: 53.5, 70.9]) vs. 60.0% [95% CI: 49.1, 70.2]).

A MAIC analysis was conducted to compare the response rates (ORR and CRR), after adjusting the clinical characteristics and disease severity on the patient population of study GCT3013-01 that overlapped with that of study GO29781 based on the inclusion criteria (N=81). Following adjustment of key baseline characteristics including age, sex, ECOG PS, disease stage, FLIPI score, prior ASCT, POD24, refractoriness to last prior therapy and to previous anti-CD20 therapy, double refractory disease, number of prior lines of therapy, and bulky disease, an ESS of 47 patients from GCT3013-01 was identified to be comparable to the 90 patients treated with mosunetuzumab in study GO29781.

Results from the MAIC analysis showed that the adjusted ORR was not significantly different between epcoritamab and mosunetuzumab (ORR 84.3% vs 80.0%, odds ratio = 1.345 [95% CI: 0.521, 3.468], p = 0.538). Although the adjusted CRR was not statistically significant, the CRR of epcoritamab was numerically higher compared to that of mosunetuzumab (CRR: 69.9% vs 60.0%, odds ratio = 1.546 [95% CI: 0.735, 3.249], p = 0.2449). The sponsor argued that this suggest that epcoritamab could potentially be a better treatment option than mosunetuzumab for this patient population.

The sponsor again used the same arguments as for tisa-cel that the efficacy data, particularly the DOR, for epcoritamab from the iNHL cohort of study GCT3013-01 was negatively affected by the COVID-19 pandemic, since it was conducted entirely at the peak of the pandemic and when the highly infectious Omicron variants were prevalent globally. In contrast, study GO29781 for mosunetuzumab was not

conducted during the COVID-19 pandemic. The median DOR and DOCR for mosunetuzumab in study GO29781 were 22.8 months and NR (at a median follow-up of 18.3 months) (Budde et al., 2022; Bartlett et al., 2022).

The sponsor also claimed that epcoritamab provided a clinically relevant advantage over mosunetuzumab based on improved safety. The overall safety profile showed higher rates of serious AEs (including related) in patients treated with epcoritamab in comparison to those treated with mosunetuzumab (69.0% [46.5%] vs. 52.3% [34.4%]). Similarly, the rate of fatal AEs was higher in patients treated with epcoritamab than those treated with mosunetuzumab (10.1% vs 1.8%). However, the sponsor again argued that the higher rates of serious AEs and fatal AEs reported for epcoritamab were mostly driven by COVID-19 infections.

According to the sponsor, comparison of individual AESIs showed that epcoritamab had a more favourable safety profile compared to mosunetuzumab. Data from the FL optimization cohort (3-step SUD regimen) showed that the rate of grade ≥ 3 CRS was lower in patients treated with epcoritamab than those treated with mosunetuzumab (0 vs. 2.2%). The rate of all grade CRS for epcoritamab was comparable to that reported for mosunetuzumab (46.7% vs. 44.4%). Furthermore, data from the 2-step SUD regimen with epcoritamab showed lower rates of neurologic events (all grade and grade ≥ 3), with 48.1% (2.3%) based on Broad definition or 31.8% (2.3%) based on Topp definition, compared to 56.5% (5%) in patients treated with mosunetuzumab, based on unspecified search criteria. The rate of grade ≥ 3 neutropenia was lower in patients treated with epcoritamab compared to mosunetuzumab (17.1% vs. 27%, respectively). The sponsor argued that the toxicities associated with mosunetuzumab may further limit use of these agents in the treatment of indolent lymphomas, especially in older patients and those with comorbidities.

Regarding the major contribution to patient care argument, the sponsor highlighted that the ease of SC administration had the advantage of significantly shorter administration time, providing a better patient experience in terms of convenience, and time spent in the clinic or infusion centre.

The sponsor used the same arguments that were given for tisa-cel regarding major contribution to patient care based on the same data sets.

The sponsor also presented a comparison of efficacy in different subgroups (data not shown). According to the sponsor, epcoritamab demonstrated consistent, robust, and clinically meaningful efficacy across prespecified subgroups of patients. Benefit was observed in traditionally hard to treat subgroups (e.g., elderly patients, patients with bulky or Ann Arbor stage III/IV disease, patients with FLIPI ≥ 3 score, patients with POD24 after first-line therapy, and patients with double refractory disease). Notably, POD24 disease has been associated with almost 80% histological transformation upon repeat biopsy, in addition to poor prognoses with traditional therapies. Epcoritamab is approved for the treatment of patients with DLBCL, including transformed FL, and may be particularly beneficial in patients with particularly high-risk disease features, including those with unidentified histologic transformation. Finally, even higher ORR and CRR were seen in patients lacking such high-risk disease characteristics, who are more representative of patients in the comparator studies as well as in the real-world setting.

COMP discussion

The data presented is considered insufficient to demonstrate an improved efficacy of epcoritamab over mosunetuzumab in patient with r/r FL. In comparison to mosunetuzumab, epcoritamab did not show improved efficacy in terms of the response rates (ORR: 80% vs. 82%, CRR: 60% vs. 62.5%, and DOR: 22.8 months vs. NR, respectively) by descriptive side-by-side treatment comparison (Table 2).

The claim of improved safety based on the frequencies of overlapping toxicities does not reflect the whole picture and biases due to differences in patient characteristic cannot be excluded. In addition, higher rates of serious AEs (including related) were reported for epcoritamab versus mosunetuzumab Given the limited experience with epcoritamab from a small single-arm study with limited follow-up, the claim of improved safety in comparison to mosunetuzumab cannot be concluded on at present stage and no adequate quantification is possible for the descriptive cross-study comparison presented.

Regarding the sponsors' arguments on the major contribution to patients care based on the route of administration, significantly shorter administration time, and time spent in the clinic or infusion centre, insufficient data have been presented supporting this claim. In a patient's satisfaction interview very few FL patients participated in this interview, and 30% dropped-out prematurely. Furthermore, the frequency of mosunetuzumab IV infusion is lower compared to epcoritamab during cycle 1-9. Hospital visits are hence more frequently required for epcoritamab than for mosunetuzumab, as the dosing schedule is more intensive than for mosunetuzumab in the first cycles. In addition, the premedication and fluid hydration recommended before administration of epcoritamab do not seem to be accounted for in the data presented. Finally, mosunetuzumab is a fixed treatment duration (8 standard cycles, with extension to 17 cycles if CR is not achieved), while epcoritamab is a continued treatment until disease progression. This may also influence patient's preference but does not seem to be considered in the interviews. A major drawback of the comparison is that it is based on estimations rather than clinical data, which are not considered reliable enough to support a claim of major contribution to patient care over mosunetuzamab.

The sponsor should further discuss the arguments for significant benefit based on a clinically relevant advantage over mosunetuzumab for the target patient population and based on updated efficacy data from the iNHL cohort of study GCT3013-01 at the latest available DCO. Conductance of an efficacy analysis in a subset of patients with r/r FL who had progressed or relapsed after prior treatment with mosunetuzumab before entering study GCT3013-01, if anyone, could be used to establish a clinically relevant advantage of epcoritamab in FL.

Significant benefit of epcoritamab versus zanubrutinib (Brukinsa)

No data was submitted to support significant benefit of epcoritamab over the Bruton's tyrosine kinase (BTK) inhibitor zanubrutinib for the treatment of patients with r/r FL.

Overall COMP conclusions

The sponsor has not provided sufficient evidence to demonstrate significant benefit of epcoritamab over tisa-cel (Kymriah), mosunetuzumab (Lunsumio), and zanubrutinib (Brukinsa) plus obinutuzumab in adult patients with r/r FL in the third- and later lines setting. The sponsor should therefore further discuss the arguments for significant benefit over these three products in patients with r/r FL and based on supplementary data.

4. COMP list of issues

The claim of significant benefit of epcoritamab over tisa-cel (Kymriah) and mosunetuzumab (Lunsumio) for the target patient population is not considered established based on the data presented.

The sponsor should provide additional data to support the claim of significant benefit for epcoritamab versus these two products in patients with r/r FL in the third- and later lines setting. Conductance of efficacy analyses in subsets of FL patients who had progressed or relapsed after prior treatment with each of the two satisfactory methods separately before entering study GCT3013-01, if anyone, could

be used to establish a clinically relevant advantage of epcoritamab in FL. The analyses should be based on updated efficacy data from the iNHL cohort of study GCT3013-01 at the most recent clinical cut-off date.

In addition, the sponsor should provide clinical data to support significant benefit of epcoritamab over the satisfactory method zanubrutinib (Brukinsa) in combination with obinutuzumab for the treatment of patients with r/r FL after two or more lines of systemic therapy.

Comments on sponsor's response to the COMP list of issues

The sponsor withdrew the application prior to the COMP opinion.