22 September 2023
EMA/OD/0000104478
EMADOC-1700519818-1128187
Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Tepkinly (epcoritamab)
Treatment of diffuse large B-cell lymphoma
EU/3/22/2581

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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Table of contents

1. Product and administrative information

Product	
Designated active substance(s)	Epcoritamab
Other name(s)	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 diffuse large B-cell 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	20 January 2022
EC decision	24 February 2022
EC registration number	EU/3/22/2581
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Johann Lodewijk Hillege / Ingrid Wang
Applicant	AbbVie Deutschland GmbH & Co. KG
Application submission	6 October 2022
Procedure start	27 October 2022
Procedure number	EMA/H/C/005985
Invented name	Tepkinly
Proposed therapeutic indication	Tepkinly as monotherapy is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy. Further information on Tepkinly 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	20 July 2023
COMP review of orphan medicinal product designation procedural history	
COMP rapporteurs	Maria Elisabeth Kalland / Frauke Naumann-Winter
Sponsor's report submission	10 November 2022
COMP discussion	13-15 June 2023
COMP opinion (adoption via written procedure)	21 July 2023

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 showing responses achieved in patients with relapsed/refractory diffuse large B-cell lymphoma;
- the condition is chronically debilitating due to involvement of single or multiple nodal or extranodal sites, including the gastrointestinal tract, the central nervous system and bone marrow and life-threatening in patients with relapsed/refractory disease;
- the condition was estimated to be affecting approximately 4 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 which demonstrated that heavily pre-treated patients with relapsed/refractory diffuse large B-cell lymphoma responded to treatment with the current product. The Committee considered that this constitutes a clinically relevant advantage.

3. Review of criteria for orphan designation at the time of marketing authorisation

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

Diffuse large B-cell lymphoma (DLBCL) is a group of fast-growing, aggressive B-cell lymphoma histologically characterised by dense proliferation of neoplastic B-cells, which typically express the B-cell markers CD19 and CD20, as well as other surface markers characteristic for the B-cell lineage (Martelli et al., 2013). It represents the most common histological subtype of non-Hodgkin's lymphomas (NHL) in adults, the 10th most common cancer in the European Union (EU), and one of the major causes of cancer-related deaths, despite advances in therapy (ECIS, 2020). It has been reported that DLBCL accounts for 25% to 45% of all NHL cases worldwide (Wild et al, 2020).

In recognition of the unique clinical and pathological features of DLBCL subtypes and associated therapeutic implications, the World Health Organisation (WHO) updated the previous 2008 classification of lymphoid neoplasms in 2016 and recently in 2022 to further refine the current understanding of mature B-cell neoplasms reflected in the recognition of 12 families of diseases under this category (Swerdlow et al., 2016; Alaggio et al., 2022). Based on a better understanding of the genetic alterations in large B-cell lymphoma (LBCL), the 4th edition of the WHO classification established a new category of high-grade B-cell lymphoma (HGBL), with rearrangements of MYC and

BCL2 and/or BCL6, so-called "double-hit" lymphomas (DHL) or "triple-hit" lymphomas (THL). In the 5th edition of the WHO classification of haematolymphoid neoplasms from 2022, the entity of HGBL with dual rearrangements of MYC and BCL2 and/or BCL6 has been renamed to DLBCL/HGBL with MYC and BCL2 rearrangements. The classification of high-grade B-cell lymphoma NOS remains the same with the updated classification (Alaggio et al., 2022). The COMP has previously accepted that these subgroups are included in DLBCL.

Patients with DLBCL often present with single or multiple rapidly enlarging symptomatic masses, with up to 40% occurring at extra-nodal sites (Martelli et al., 2013). The disease usually affects adults, especially around the age of 60 to 70 years with a median age of 66 years at diagnosis, but it also rarely occurs in adolescents and children. It is slightly more frequent in men than in women (Mounier et al., 2015).

The approved therapeutic indication "*Tepkinly as monotherapy is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy*" falls within the scope of the designated orphan condition "Treatment of diffuse large B-cell lymphoma".

Intention to diagnose, prevent or treat

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

Chronically debilitating and/or life-threatening nature

The sponsor focused on the life-threatening nature of the relapsed/refractory (r/r) disease and that the prognosis for patients whose disease is refractory or who relapse within 12 months after receiving high doses of chemotherapy (HDT) followed by autologous stem cell transplantation (ASCT) is extremely poor, with an overall response rate (ORR) of 26%, a complete response rate (CRR) of 7% to subsequent treatment, and median overall survival (OS) of 6.3 months (Crump et al., 2017). With each successive line of therapy, patients with r/r disease experience decreased response rates and shortened responses.

The sponsor has not identified any significant changes in the seriousness of DLBCL since the orphan designation was granted in 2022. The COMP has previously accepted that the clinical course of DLBCL can be chronically debilitating due to constitutional symptoms, local symptoms of lymphadenopathy, end-organ damage from disease involvement, and bone marrow failure that may lead to infections, anaemia, and thrombocytopenia, and life-threatening in patients not responding to treatment. The severe nature of DLBCL earlier acknowledged by the COMP remains acceptable for this procedure.

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 in 10,000 persons in the EU. This estimate has now been updated:

The sponsor used the following publicly available data sources to derive and report all prevalence and incidence data:

- The European Cancer Information System (ECIS; 2020 data)

- The International Agency for Research on Cancer's (IARC's) Global Cancer Observatory (GCO, formerly GLOBOCAN; 2020 data)
- The Haematological Malignancy Research Network (HMRN; 2004-2016 data)

The Eurostat database (EC, 2022) was used as the source of total population data.

Given the similarity in healthcare practice and population characteristics between UK and EU countries, and comparable risks for and survival of NHL between UK and EU populations, and the lack of DLBCL specific data for EU countries, the sponsor argued that the HMRN data could be used to estimate the prevalence of DLBCL in the EU+3 European Economic Area (EEA) countries. The robustness of the HMRN database is acknowledged by the COMP and can be considered supportive for a conclusion on the prevalence.

The sponsor also claimed that there is no 'complete' prevalence directly reported for either DLBCL or NHL which are available from published literature or databases and therefore, a 10-year partial prevalence was used for the calculation. It should be noted that this is not correct since complete prevalence for DLBCL are directly reported by the Italian population-based cancer registry Italian Association of Cancer Registries (AIRTUM) and complete prevalence for NHL can be extracted from the German cancer registry Robert Koch Institute, the Spanish Registry (REDECAN), and the national Slovenian Cancer Registry. In addition, 20-year partial prevalence for NHL are accessible from both the Integraal Kankercentrum Nederland (IKNL, The Netherlands) and Association of the Nordic Cancer Registries (NORDCAN; Nordic countries: Denmark, Faroe Islands, Finland, Greenland, Iceland, Norway, and Sweden). Nevertheless, it can be agreed that the whole DLBCL population would be best reflected in the calculation if a 10-year limited duration estimate is used since the cumulative relapse for DLBCL has been reported to peak at around 6-8 years and plateau thereafter (Maurer et al., 2014; Harrysson et al., 2021).

As the referenced databases (ECIS and IAR's GCO) do not identify DLBCL but only NHL, assumptions were required regarding the percentage of total NHL cases that comprised the DLBCL subtype. Published proportion of DLBCL cases among all NHL cases varied from 22.8% (Mounier et al., 2015; EUROCARE data pool) to 47.8% (Smith et al., 2015; UK HMRN). Given the variations in the reported estimates of the proportion of DLBCL among NHL patients and potential improvement of survival in NHL patients in the last decade, the sponsor chose to use the updated data from the HMRN database in the sponsor's estimation of DLBCL proportion among all NHL cases. The following subtypes were included in the estimated DLBCL proportion: DLBCL not otherwise specified (DLBCL, NOS), T-cell/histiocyte-rich large B-cell lymphoma, primary DLBCL of the CNS, primary cutaneous DLBCL, leg type, primary mediastinal large B-cell lymphoma (PMBCL), intravascular large B-cell lymphoma, and -cell lymphoma, and plasmablastic lymphoma. This is however, a very wide definition as some of these subtypes are not regarded as DLBCL according to the 5th edition of the WHO classification of haematolymphoid tumours (WHO-HAEM5) of the type of lymphoid neoplasms from 2022 (Alaggio et al., 2022), but rather considered as separate conditions. The COMP would for example designate PMBCL as a separate condition. Moreover, the COMP has recently agreed to use a ratio of around 35% as a reasonable figure for the percentage of DLBCL within all NHL cases.

The sponsor used two different approaches to estimate the prevalence of DLBCL per 10,000 persons in the EU+3 EEA countries:

In the first approach, the DLBCL prevalence was estimated by multiplying the calculatedDLBCL incidence by country and sex for each of the countries based on data from ECIS and HMRN with the

estimated disease duration (P = ECIS I [NHL*ratio] x HMRN D). The proportions of DLBCL within all NHL cases among incident cases in HMRN were assumed to be 44.6% for males and 46.3% for females. The DLBCL duration were calculated to be around 5.11-5.14 years. The prevalence of DLBCL usingthis method was estimated to **4.50** per 10,000 people in the EU+3 EEA countries in 2020.

In the second approach, the DLBCL prevalence was estimated by applying the ratio of 10-year to 5-year prevalence of NHL from HMRN and the prespecified proportion of DLBCL within all NHL cases from the HMRN to the 5-year NHL prevalence estimates from IARC's GCO. The ratios of 10-year to 5-year NHL prevalence were assumed to be 1.6-1.7. The proportion of DLBCL within all NHL cases among prevalent cases in HMRN was around 40.0%. The estimated number of prevalent cases of DLBCL was then calculated using the prevalence rate of DLBCL multiplied by the corresponding population size, for each country by sex. The 10-year prevalence of DLBCL from the second approach was estimated to be **4.06** per 10,000 people in EU+3 EEA countries in 2020.

The sponsor does not conclude on which option of the two estimates is the preferred one. Both proposed values are broadly in line with prevalence figures recently accepted by the COMP for DLBCL, however, the COMP would like to use an estimate of 4.3 in 10,000 persons for this maintenance procedure based on recently available epidemiological data for a 10-year limited-duration prevalence obtained from population-based cancer registries (i.e., NORDCAN, the IKNL, Slovenia Cancer Registry, Robert Koch Institute, Belgium Cancer Registry).

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 has summarised all available therapies and newer treatment options authorised for the treatment of DLBCL in the EU. The European Society for Medical Oncology (ESMO) clinical practice guidelines for diagnosis, treatment, and follow-up of DLBCL describe some of the treatment strategies available in the first- and second line setting (Tilly et al., 2015). There is currently no established standard of care according to the ESMO guidelines for patients who have been treated with more than two prior systemic therapies. However, the treatment landscape has evolved since the ESMO guidelines became publicly available, and new medicines such as polatuzumab (Polivy), tafasitamab (Minjuvi), the CAR-T cell therapies axicabtagene ciloleucel (hereinafter referred to as axi-cel; Yescarta), tisagenlecleucel (hereinafter referred to as tisa-cel; Kymriah), and lisocabtagene maraleucel (hereinafter referred to as liso-cel; Breyanzi), and loncastuximab tesirine (Zynlonta) have been authorised in the EU after 2015. These products are therefore not included in the current ESMO guidelines.

The sponsor's product Tepkinly (epcoritamab) is intended to treat adult patients with r/r DLBCL who have received two or more prior lines of systemic therapy. A summary of medicinal products approved in the EU for r/r DLBCL and NHL in the third- and later lines setting, and whether they are considered relevant for a discussion on the significant benefit of Tepkinly in patients with r/r DLBCL is given below.

Table 1. EU approved products for the treatment of adults with r/r DLBCL in the 3L+ setting

EU Centralised number; MA	Product name (INN)	Approved therapeutic indication	Significant benefit discussion needed
EMEA/H/C/002055; 10/05/2012	Pixuvri (pixantrone dimaleate)	Pixuvri is indicated as monotherapy for the treatment of adult patients with multiply r/r aggressive NHL. 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.	No, covers only r/r NHL patient in the third- and fourth line setting for those who are refractory to last therapy
EMEA/H/C/004870; 16/01/2020	Polivy (polatuzumab vedotin)	Polivy in combination with bendamustine and rituximab is indicated for the treatment of adult patients with r/r DLBCL who are not candidates for haematopoietic SCT.	No, covers only r/r DLBCL patient who are ineligible to HSCT
EMEA/H/C/005436; CMA 26/08/2021	Minjuvi (tafasitamab)	Minjuvi is indicated in combination with lenalidomide followed by tafasitamab monotherapy for the treatment of adult patients with r/r DLBCL who are not eligible for ASCT.	No, covers only r/r DLBCL patient who are ineligible to ASCT
EMEA/H/C/004090; 23/08/2018	Kymriah (tisagenlecleucel)	Kymriah is indicated for the treatment of adult patients with r/r DLBCL after two or more lines of systemic therapy.	Yes, as there is a complete overlap with the proposed therapeutic indication of epcoritamab
EMEA/H/C/004480; 23/08/2018	Yescarta (axicabtagene ciloleucel)	Yescarta is indicated for the treatment of adult patients with r/r DLBCL and PMBCL, after two or more lines of systemic therapy.	Yes, as there is a complete overlap with the proposed therapeutic indication of epcoritamab
EMEA/H/C/004731; 04/04/2022	Breyanzi (lisocabtagene maraleucel)	Breyanzi is indicated for the treatment of adult patients with r/r DLBCL, PMBCL and FL3B, after two or more lines of systemic therapy.	Yes, as there is a complete overlap with the proposed therapeutic indication of epcoritamab
EMEA/H/C/005685; CMA 20/12/2022	Zynlonta (loncastuximab tesirine)	Zynlonta as monotherapy is indicated for the treatment of adult patients with	Yes, as there is a complete overlap with the proposed

EU Centralised number; MA	Product name (INN)	Approved therapeutic indication	Significant benefit discussion needed
		r/r DLBCL and HGBL, after two or more lines of systemic therapy	therapeutic indication of epcoritamab

MA: marketing authorisation; CMA: conditional MA; SCT: stem cell transplant; ASCT: autologous SCT; 3L+: third- and later lines; PMBCL: primary mediastinal large B-cell lymphoma; FL3B: follicular lymphoma grade 3B; HGBL: high-grade B-cell lymphoma.

The sponsor also included a discussion regarding glofitamab (Columvi) in the submission. Glofitamab has the same bispecific targets as epcoritamab (Tepkinly), but at the time of COMP opinion for this procedure, a notification of the marketing authorisation of Columvi had not been published in the *Official Journal of the European Union* (Commission notice on the application of Articles 3, 5 and 7 of Regulation (EC) No 141/2000 on orphan medicinal products (2016/C 424/03)), and therefore Columvi is not considered to be a satisfactory method for patients with r/r DLBCL within this procedure.

In conclusion, the approved CAR-T cell products in the third- and later lines setting, specifically Yescarta, Kymriah, and Breyanzi, as well as Zynlonta are considered satisfactory methods of treatment relevant for a discussion on the significant benefit for Tepkinly in DLBCL and will be further discussed below.

Significant benefit

The sponsor has sought scientific advice from national competent authorities as well as centrally from EMA but did not ask any question on how to collect the evidence needed to justify significant benefit.

Epcoritamab (GEN3013; DuoBody®-CD3xCD20) is a bispecific T-cell engager that recognizes the T-cell antigen CD3, as well as the B-cell antigen CD20. According to the sponsor, epcoritamab introduces a novel mechanism of action into the existing r/r DLBCL treatment landscape and provides a significant benefit by offering a clinically relevant advantage and a major contribution to patient care compared to existing therapies. The sponsor specifically argued that epcoritamab has demonstrated significant benefit based on a clinically relevant advantage in terms of improved efficacy and better safety in comparison to Kymriah and Zynlonta, and comparable efficacy but improved safety versus Yescarta and Breyanzi for r/r DLBCL patients in the third- and later lines setting. It is also claimed that epcoritamab provides a benefit to patients who have already received the approved CAR-T cell products and a major contribution to patient care by being readily available as an off-the-shelf immunotherapy when needed to patients with a highly aggressive and rapidly progressing disease in urgent need for treatment, and through the route of administration which is subcutaneously (SC) contrary to other available therapies that are typically administered intravenously (IV).

The claim of significant benefit is based on the results from an ongoing, global, multi-cohort, open-label, first-in-human (FIH), single-arm phase 1/2 study GCT3013-01, which is used to obtain the pivotal evidence for epcoritamab in patients with r/r DLBCL after at least two prior lines of systemic therapy in the conditional marketing authorisation application. The efficacy data consisted of 139 subjects with r/r DLBCL from the pivotal aggressive NHL (aNHL) expansion part (n=157) of the study, where 69.8% (97/139) of them had de novo disease and 28.8% (40/139) had a transformed disease at study entry. The aNHL cohort also included 16 patients who were identified as double-hit (DH)/triple-hit (TH) lymphoma (as assessed by central/local fluorescence in situ hybridization [FISH]

analysis). The data cut-off (DCO) date for the efficacy and safety analyses provided was 30-Jun-2022. At the DCO, the median duration of study follow-up was 15.7 months (range: 14.9, 16.6), whereas the median number of epcoritamab cycles initiated in the study was 5 (range: 1, 26).

The primary efficacy objective of the aNHL 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 DLBCL, 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), 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 age of the patients with r/r DLBCL in the aNHL cohort was 66 years (range: 22-83), and 20.9% (29/139) of subjects were ≥75 years of age. The median number of prior lines of anti-lymphoma therapy in the DLBCL cohort was 3 (range: 2-11). A total of 70.5% of subjects had at least 3 prior lines of systemic therapy. All patients had received prior chemotherapy, anti-CD20 monoclonal therapy, and alkylating-containing agents. Overall, 59.0% (82/139) of the subjects had primary refractory disease, 74.8% (104/139) were refractory to 2 consecutive lines of prior anti-lymphoma therapy, 82.0% (114/139) were refractory to their last line of systemic antineoplastic therapy. Over one third (38.1%; 53/139) of the subjects had previously received CAR-T cell therapy before study entry, among whom 73.6% (39/53) were refractory to this therapy.

Clinically meaningful responses as characterized by ORR of 61.9% (86/139; 95% confidence interval [CI]: 53.3, 70.0) and CRR of 38.8% (54/139; 95% CI: 30.7, 47.5) were observed. The responses to epcoritamab occurred early in treatment, with a median TTR of 1.4 months (range: 1.0, 8.4) and median time to complete response (TTCR) of 2.6 months (range: 1.2, 10.2) in patients with DLBCL, correlating with the first and second postbaseline scan, respectively. The responses were also durable and the median DOR per IRC-assessment was 15.6 months (95% CI: 9.7, not reached [NR]). The median DOR among complete responders was 17.3 months (95% CI: 15.6, NR). After a median study follow-up of 15.7 months (range: 14.9, 16.6), the median IRC-assessed PFS in patients with DLBCL was 4.4 months (95% CI: 3.0, 8.8) and median OS was 18.5 months (range: 11.7, NR).

Significant benefit based on a clinically relevant advantage

Summaries of selected baseline characteristics of the study populations which formed the basis for the EU approvals of Yescarta, Kymriah, Breyanzi, and Zynlonta in patients with r/r DLBCL in the third- and later lines setting were provided along with key efficacy results from the pivotal comparator studies as compared to data for epcoritamab from study GCT3013-01 (Table 2 and Table 3).

Table 1. Comparison background patient population for patients with DLBCL enrolled in study GCT3013-01 (epcoritamab) versus pivotal studies of satisfactory methods in the EU

Drug Name (Trade Name)	Epcoritamab[a]	Yescarta[b]	Kymriah[c]	Breyanzi[d]	Zynlonta[e]
Background Patient Population					
N	139	101	99	229	145
Median age (range)	66 (22,83)	58 (23,76)	56 (22,76)	62 (18,82)	66 (23,94)
Age ≥ 65 years, %	52.6	24	23.2	38.9	55.2
Number of Prior Lines of Therapy					
1	0	2	5.1	NL	0
2	30.2	29	44.4	NL	43.4
≥ 3 (3, > 3)	68.9 (32.4, 37.4)	70 (30,40)	51.4 (31.3,19.1)	NL	56.5 (24.1,32.4)
Prior ASCT therapy (%)	18.7	25	47.5	36.7	16.6
Prior CAR T (%)	38.1	0	0	0	9
Primary refractory (%)	59	2	NL	NL	20
Refractory to ≥ 2 LOT (%)	74.8	76	NL	NL	NL
Refractory to last LOT (%)	82	NL	54.8	NL	60.7

aNHL = aggressive non-Hodgkin lymphoma; ASCT = autologous stem cell transplant; BR = bendamustine and rituximab; CAR T = chimeric antigen receptor T-cell therapy; DLBCL = diffuse large B-cell lymphoma; EU = European Union; LOT = line of therapy; NL = not listed; R-GemOx = rituximab, gemcitabine, and oxaliplatin; R/R = relapsed/refractory.

a. From the updated analysis of 139 subjects with DLBCL from the pivotal aNHL expansion cohort (n = 157) of GCT3013-01 trial (clinical DCO: 30 June 2022).
b. Yescarta assessment report (EMA/481168/2018) was used as a source for background patient population. Trial was based on 101 patients with refractory LBCL with 77 (76%) subjects with DLBCL, 8 (8%) subjects with PMBCL, and 16 (16%) subjects with TFL.
c. Kymriah assessment report (EMA/485563/2018) was used as a source for background patient population.
d. Breyanzi SmPC was used as a source for background patient population. Trial was based on large B-cell lymphoma cohort (n = 229) consisted of 117 (51.1%) subjects with DLBCL NOS, 60 (26.2%) subjects with transformed from indolent lymphomas, 33 (14.4%) subjects with HGBCL, 15 (6.6%) subjects with PMBCL, and 4 (1.8%) subjects with FL Grade 3B. The median number of prior lines of therapy was 3 (range: 1, 8).
e. Zynlonta assessment report (EMA/CHMP/834750/2022) was used as a source for background patient population. Trial was based on n = 145 subjects with DLBCL including with 127 (87.6%) subjects with DLBCL NOS, 11 (7.6%) subjects with HGBCL, and 7 (5%) subjects with primary mediastinal DLBCL.

The sponsor argued that the ORR achieved with epcoritamab in study GCT3013-01 (61.9% [95% CI: 53.3, 70.0]) is numerically higher than those achieved with Zynlonta (ORR of 48.3% [95% CI: 39.9, 56.7]) and Kymriah (ORR of 51.6% [95% CI: 41.0, 62.1]). The ORR for the CAR T-naïve subgroup in study GCT3013-01 for epcoritamab (67% [95% CI: 56, 77]) is comparable to the ORR observed with Yescarta (ORR of 72% [95% CI: 62, 81]) and Breyanzi (ORR of 72.7% [95% CI: 66.2, 78.5]), based on the largely overlapping confidence intervals.

The responses are approximately as durable as after treatment with the other satisfactory methods, although duration of follow-up is quite different between the studies. The sponsor stated that DOR data for epcoritamab are mature as the median DOR did not change with additional 5 months of follow-up (DCO: 18-Nov-2022). It is worth noting that in the cross-study comparisons, the follow-up times of the other comparator products are substantially different (shorter) and some results are even not available or listed.

Table 2. Efficacy comparison of epcoritamab versus satisfactory methods for r/r DLBCL

Drug Name (Trade Name)	Epcoritamab[a]	Yescarta[b]	Kymriah[c]	Breyanzi[d]	Zynlonta[e]
Approval Type	NA	full	full	full	conditional
MoA	Bispecific Ab	CAR T	CAR T	CAR T	ADC
RoA	SC	IV	IV	IV	IV
Efficacy Analysis					
Response evaluable set (N)	139	101	93	216	145
ORR %	61.9	72	51.6	72.7	48.3
CRR %	38.8	51	39.8	53.2	24.1
Median DOR (months)	15.6	14	13.9	20.2	13.4
Median PFS (months)	4.4	NL	NL	NL	4.93
Median OS (months)	18.5	NR	11.7	NL	9.53
Median Follow-up (months)	15.7	15.1	7.7	19.9	7.8

Ab = antibody ADC = antibody drug-conjugate; aNHL = aggressive non-Hodgkin lymphoma; BR = bendamustine and rituximab; CAR T = chimeric antigen receptor T-cell therapy; CR = complete response; DLBCL = diffuse large B-cell lymphoma; DOR = duration of response; EoT= End of Treatment; EU = European Union; IRC = independent review committee; IV = intravenous; IWG = international working group; mAb = monoclonal antibody; MoA = mechanism of action; NL = not listed; ORR = overall response rate; OS = overall survival; PFS = progression-free response; R-GemOx = rituximab, gemcitabine, and oxaliplatin; RoA = route of administration; R/R = relapsed/refractory; SC = subcutaneous.

a. From the updated analysis of 139 subjects with DLBCL from the pivotal aNHL expansion cohort (n = 157) of GCT3013-01 trial (clinical DCO: 30 June 2022). Responses were based on ORR and CR, as determined by IRC, Lugano response criteria.[4]
b. Yescarta SmPC was used as a source for efficacy analysis. Responses were reported at 12-month analysis with ORR and CR based on IRC. Trial was based on 101 patients with refractory LBCL with 77 (76%) subjects with DLBCL, 8 (8%) subjects with PMBCL, and 16 (16%) subjects with TFL.
c. Kymriah assessment report (EMA/485563/2018) was used as a source for efficacy analysis (DCO: 08 Dec 2017). Efficacy analysis set (n = 93) included subjects infused with tisagenlecleucel, followed for at last 3 months of discontinued later. DOR was calculated based on 48 subjects, and OS was calculated based on the full analysis set of 111 subjects which included all patients infused with Kymriah. Responses were based on best ORR and CR as determined by IRC, Lugano response criteria.[4]
d. Breyanzi SmPC was used as a source for efficacy analysis. Responses were based on best ORR and CR as determined by IRC, Lugano response criteria.[4] Trial was based on large B-cell lymphoma cohort (n = 229) consisted of 117 (51.1%) subjects with DLBCL NOS, 60 (26.2%) subjects with transformed from indolent lymphomas, 33 (14.4%) subjects with HGBCL, 15 (6.6%) subjects with PMBCL, and 4 (1.8%) subjects with FL Grade 3B.
e. Zynlonta SmPC was used as a source for efficacy analysis. The primary endpoint was ORR defined as proportion of subjects with best overall response of CR or PR according to 2014 Lugano classification, determined by central review. Median OS and PFS were obtained from the Assessment report (EMA/CHMP/834750/2022). Trial was based on n = 145 subjects with DLBCL including with 127 (87.6%) subjects with DLBCL NOS, 11 (7.6%) subjects with HGBCL, and 7 (5%) subjects with primary mediastinal DLBCL.

The sponsor has conducted indirect treatment comparisons (ITC) on selected efficacy endpoints, including best response rates (ORR and CRR) and survival outcomes (PFS and OS), to estimate the comparative efficacy of epcoritamab versus each of the satisfactory methods of treatment for patients with r/r LBCL and DLBCL after at least two prior lines of therapy, based on an unanchored matching-adjusted indirect comparison (MAIC) methodology. The relative efficacy of epcoritamab in terms of DOR was not assessed using MAIC.

In accordance with the recommendations of the National Institute for Health and Care Excellence (NICE) guidance on population-adjusted indirect comparisons based on propensity score reweighting methods (Philippo, 2016), a MAIC approach was taken to compare the patient-level data of subjects with r/r DLBCL after two or more prior lines of therapy from study GCT3013-01 for epcoritamab with aggregate patient data from published data from the pivotal comparator studies ZUMA-1 for Yescarta (Neelapu et al., 2017), JULIET for Kymriah (Schuster et al., 2019), TRANSCEND for Breyanzi (Abramson et al., 2020), and LOTIS-2 for Zynlonta (Caimi et al., 2021).

In order to allow for a more balanced data comparison across epcoritamab and other therapies in terms of CAR-T cell eligibility and prior CAR-T cell exposure, three distinct study populations in study GCT3013-01 were explored: the overall study population, CAR-T cell naïve subgroup, and CAR-T cell eligible subgroup. One study for each satisfactory method was selected for inclusion within the MAIC if it met the following criteria: 1) included subjects on at least two prior lines of therapy, 2) reported baseline clinical characteristics, 3) included Kaplan-Meier PFS and OS graphs that clearly displayed the survival and progression events, and 4) reported outcomes that were defined similarly to those in study GCT3013-01. It was noted by the COMP that no information on robustness, sensitivity analyses, weights, and so forth was submitted for the MAIC analyses.

The selection of patient characteristics that are either known or plausible potential effect modifiers for adjustment was determined based on review of the literature, empirical testing of prognostic status in study GCT3013-01, and clinical expert input as to which baseline patient characteristics are important confounders (prognostic factors and effect modifiers) to adjust for in the r/r DLBCL population. The final list of validated variables that were considered for adjustment based on feedback from clinical experts in the UK during a consultation included the following key variables: age ≥65 years, sex, DLBCL histology (including transformed follicular lymphoma) versus not DLBCL histological subtype, primary refractoriness, refractoriness to ≥ 2 consecutive lines of therapy, refractoriness to last prior anti-CD20 agent, refractoriness to last treatment when information on last prior anti-CD20 or primary refractoriness is not available, exposure to prior CAR-T cell therapy, prior ASCT, relapse within 12 months of ASCT, Eastern Cooperative Oncology Group (ECOG) performance status (PS) >1, and disease stage III-IV. Of note, IPI score was considered not needed for adjustment, if disease stage is already included for adjustment, as IPI score is already correlated with disease stage.

The COMP decided that MAICs of the time-to-event outcomes of PFS and OS were not considered reliable because these endpoints were collected from independent single-arm studies where selection bias could not be assessed. Therefore, these comparisons will not be reflected in detail in this report.

Significant benefit of epcoritamab over Yescarta based a clinically relevant advantage

The efficacy of Yescarta in patients with r/r DLBCL, HGBCL and PMBCL was evaluated in the pivotal, multicentre, open-label, single-arm phase 1/2 study ZUMA-1 (N=101, modified intention-to-treat [mITT] population). The sponsor provided an indirect comparison of efficacy data in **CAR-T cell naïve subjects** with r/r DLBCL treated with epcoritamab versus patients who received Yescarta in ZUMA-1. The response rates achieved with epcoritamab (67% for ORR and 42.2% for CRR) in 86 CAR-T cell naïve subjects with DLBCL were numerically lower compared to those obtained with Yescarta (72% for ORR and 51% for CRR) in 101 CAR-T cell naïve (LBCL subjects at a median follow-up of 15.1 months.

The MAIC results in both the CAR-T cell naïve subgroup and CAR-T cell eligible subgroup from study GCT3013-01 showed that epcoritamab compared to Yescarta resulted in comparable response rates and a trend towards longer survival in patients with r/r DLBCL. Following adjustments of the baseline characteristics, including age, sex, ECOG PS, disease stage, primary refractory disease, and refractory to ≥ 2 consecutive lines of therapy, and relapse within 12 months of ASCT, an effective sample size (ESS) of 27 subjects from GCT3013-01 was compared to the 101 subjects treated with Yescarta in ZUMA-1. The adjusted response rates with epcoritamab (73.4% for ORR and 48.5% for CRR) in the CAR-T cell naïve subjects were comparable to those with Yescarta (74.3% for ORR and 54.5% for CRR) ($p = 0.927$ and $p = 0.853$, respectively

The sponsor also provided another MAIC of efficacy data in **CAR-T cell eligible subjects** who were treated with epcoritamab versus those treated with Yescarta. This second MAIC assessed the outcomes

for the 50 DBLCL subjects who would be considered CAR-T cell eligible within the subgroup of 86 CAR-T cell naïve subjects within study GCT3013-01. The CAR-T cell eligible subgroup in GCT3013-01 was identified using the eligibility and exclusion criteria as defined in the ZUMA-1 protocol and additional haemoglobin and lactase dehydrogenase parameters in the Swedish CAR-T guidelines. Following adjustment of the baseline characteristics, an ESS of 21 patients was compared to the 101 patients treated in ZUMA-1. The adjusted response rates with epcoritamab (72.7% for ORR and 50.9% for CRR) in the CAR-T cell eligible subjects were comparable to those with Yescarta (74.3% for ORR and 54.5% for CRR) ($p = 0.576$ and $p = 0.873$, respectively).

Of the 53 patients who had received prior CAR-T cell therapy in study GCT3013-01, 21 patients were previously treated with Yescarta. According to the sponsor, the efficacy data for epcoritamab showed clinical meaningful and durable responses, with an ORR of 38.1% (8/21; 95% CI: 14.7, 94.7) and a CRR of 19.0% (4/21; 5.4, 41.9) in the DLBCL patients who had previously been treated with Yescarta. The median DOR among the responders to epcoritamab in this subgroup of patients was 7.6 months (95% CI: 0.8, not reported [NR]). It should be noted that the efficacy observed in these patients was generally lower than the results reported in the overall DLBCL cohort. In addition, there is uncertainty in the point estimates for the observed responses as indicated by their wide 95% CIs.

The data presented **do not indicate an improved efficacy of epcoritamab over Yescarta** in DLBCL. In addition, the MAIC approach led to substantial reductions in the ESS for the MAICs, with a down-weighting of more than 70% of the DLBCL cohort in study GCT3013-01 for the adjusted CAR-T cell naïve and CAR-T cell eligible populations compared to the mITT population from ZUMA-1. The MAIC results are consequently difficult to interpret and are not considered sufficiently robust and reliable.

Although the responses observed in patients who had progressed following treatment with Yescarta could be considered to constitute a clinically relevant advantage for patients with r/r DLBCL in the third- and later lines setting, the numbers of patients exposed to Yescarta and those responding to epcoritamab is limited and the data appears to be immature. The sponsor should therefore provide updated sub-analysis of all efficacy parameters measured and available to date for all patients who had progressed or relapsed after prior treatment with Yescarta in the DLBCL cohort of study GCT3013-01.

The sponsor also argued that the overall safety profile showed a lower proportion of patients with Grade ≥3 adverse events (AEs) with epcoritamab in study GCT3013-01 (62.9%) in comparison to those treated with Yescarta in ZUMA-1 (98.1%). The rate of serious AEs (SAEs) with epcoritamab was comparable to those observed in patients treated with Yescarta (58.1% versus 52%). On the contrary, the rate of fatal AEs was higher for those patients treated with epcoritamab in study GCT3013-01 (7.2%) versus patients treated with Yescarta in ZUMA-1 (3.9%).

When comparing overlapping toxicities, Grade ≥3 CRS and neurological toxicity in patients treated with epcoritamab compared favourably with the rates reported with Yescarta in ZUMA-1. Grade ≥3 CRS rate was 2.4% with epcoritamab versus 13% with Yescarta, and any Grade CRS rates were also lower with epcoritamab than Yescarta (50.3% vs. 93%). Furthermore, Grade ≥3 neurological toxicities were lower with epcoritamab (4.2% based on Broad definition or 1.8% based Topp definition) than with Yescarta (28%). Any Grade neurotoxicity rates were also lower with epcoritamab (35.3% broad definition; 25.7% Topp definition) than Yescarta (64%). Moreover, the rate of patients with Grade ≥3 infection was higher in patients treated with Yescarta (26%) versus those treated with epcoritamab (14.4%).

The sponsor noted that different grading criteria for CSR and neurological toxicity was used in the clinical studies, and that the presented cross-study comparisons should hence be interpreted with

caution. ASTCT Lee 2014 grading criteria was used in ZUMA-1 (Lee et al., 2014), which had different thresholds and criteria than ASTCT Lee 2019 criteria used in study GCT3013-01 with epcoritamab (Lee etal., 2019). The threshold for Grade 3 CRS is lower with ASTCT Lee 2019, signalling the possibility that Grade ≥3 CRS cases may be higher in ZUMA-1 based on more current grading criteria. Similarly, the terminology of ICANS AE was defined only recently in the ASTCT 2019 Lee criteria, and therefore may not have been categorized as neurologic toxicity AEs in ZUMA-1. The same arguments apply to the pivotal studies for the two other approved CAR-T cell products.

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. Moreover, a comparable proportion of patients experienced SAEs across the two pivotal studies. Given the limited experience with epcoritamab from a small single-arm study with limited follow-up, the claim of a better safety profile in comparison to Yescarta cannot be concluded on at present stage and no adequate quantification is possible for the descriptive cross-study comparisons presented.

Significant benefit of epcoritamab over Kymriah based on a clinically relevant advantage

The efficacy of Kymriah in patients with r/r DLBCL who had received two or more lines of therapy was evaluated in the pivotal, global, multicentre, open-label, single-arm phase 2 study JULIET (N=115, mITT). The sponsor provided an indirect comparison of response rates with epcoritamab (67% for ORR and 42.2% for CRR) in the 86 **CAR-T cell naïve subjects** with r/r DLBCL from study GCT3013-01, which were higher compared to those obtained with Kymriah (51.6% for ORR and 39.8% for CRR) in 99 CAR-T cell naïve subjects with r/r DLBCL from JULIET.

After a median duration of study follow-up of 15.7 months (DCO: 30-Jun-2022), the median DOR in patients with r/r DLBCL treated with epcoritamab was 15.6 months (95% CI: 9.7, NR). The median DOR in patients treated with Kymriah was shorter at 13.9 months (95% CI: 7.2, NE). It should be noted that the response rates to Kymriah was reported to be slightly higher at the latest DCO of its pivotal study (54.5% for ORR and 41.4% for CRR) with a median duration of study follow-up of 7.7 months (range: 0.4-50.0). The median DOR was not yet reached at this DCO.

The MAIC results showed that epcoritamab resulted in significantly higher responses compared to Kymriah in CAR-T cell naïve patients with r/r DLBCL. Following adjustments of the baseline characteristics, including age, sex, disease stage, refractoriness to last therapy, and prior ASCT, an ESS of 28 CAR-T cell naïve subjects was compared to the 115 subjects in JULIET. Compared to treatment with Kymriah, epcoritamab resulted in significantly higher responses in the CAR-T cell naïve subjects with r/r DLBCL. The unadjusted and adjusted **ORR were significantly higher with epcoritamab** in the CAR-T cell naïve patient subgroup (67.4% and 78.8%, respectively) versus Kymriah (53.0%) ($p = 0.0378$ and $p = 0.00123$, respectively). Similarly, the unadjusted and adjusted CRR were numerically higher with epcoritamab (41.9% and 55.0%, respectively) than with Kymriah (39.1%) ($p = 0.698$ and $p = 0.118$, respectively).

A second MAIC was conducted to assess the efficacy of epcoritamab in the 50 patients with r/r DBLCL who would be considered **CAR-T cell eligible subjects** within the subgroup of 86 CAR-T cell naïve patients from study GCT3013-01 versus those treated with Kymriah in JULIET. Following adjustments of the baseline characteristics, an ESS of 20 CAR-T cell eligible subjects was compared to the 115 subjects in JULIET. The unadjusted and adjusted **ORR were significantly higher with epcoritamab** in the CAR-T cell eligible patient subgroup (72.0% and 80.7%, respectively) versus that reported for Kymriah (53.0%) ($p = 0.0175$ and $p = 0.0016$, respectively). Similarly, both the unadjusted and

adjusted CRR were numerically higher with epcoritamab (52.0% and 61.7%, respectively) versus Kymriah (39.1%), with the CRR in the adjusted population being statistically significant (p = 0.0401).

The efficacy data for epcoritamab also demonstrated a clinical benefit in the 22 patients with r/r DLBCL who had received Kymriah before study entry, with an ORR of 59.1% (13/22; 95% CI: 36.4, 79.3) and a CRR of 40.9% (9/22; 95% CI: 20.7, 63.6), which were consistent with the response rates reported for the overall DLBCL cohort of study GCT3013-01. Although the median DOR among the responders was not yet reached, the estimated percentage of patients remaining in response at 9 and 12 months were 76.9% (95% CI: 44.2, 91.9), and 76.9% (95% CI: 44.2, 91.9), respectively.

The indirect treatment comparisons presented **support the claim of an improved efficacy of epcoritamab over Kymriah**. Furthermore, the efficacy analysis in the subset of patients with prior CAR-T cell therapy in the DLBCL cohort of study GCT3013-01 showed that epcoritamab offered a clinical benefit for those patients who have progressed or relapsed after prior treatment with Kymriah, as they achieved high and sustained ORR and CRR to epcoritamab. The responses observed in this subgroup of patients could be considered to constitute a clinically relevant advantage for patients with r/r DLBCL in the third- and later lines setting although the data on the time-dependent endpoints were still immature.

Significant benefit of epcoritamab over Breyanzi based on a clinically relevant advantage

The efficacy of Breyanzi in patients with r/r DLBCL, HGBCL, PMBCL, and FL grade 3b who had received at least two lines of prior therapy was evaluated in the pivotal, global, multicentre, open-label, single-arm phase 1 study TRANSCEND (N=269; mITT). The sponsor considered that epcoritamab showed comparable efficacy outcomes compared to Breyanzi based on indirect comparisons between CAR-T cell naïve patients within study GCT3013-01 treated with epcoritamab and patients who received Breyanzi in TRANSCEND. The response rates achieved with epcoritamab in the 86 **CAR-T cell naïve subjects** with r/r DLBCL from study GCT3013-01 (67% for ORR and 42.2% for CRR) were lower compared to those reported for Breyanzi in 216 CAR-T cell naïve LBCL subjects from TRANSCEND (72.7% for ORR and 53.2% for CRR).

The MAIC results showed that epcoritamab resulted in comparable efficacy as compared to Breyanzi in CAR-T cell naïve patients with r/r DLBCL. Following adjustments of the baseline characteristics, including age, sex, ECOG PS, refractoriness to subsequent line of therapy (subjects who never achieved CR with previous therapy), and prior ASCT, an ESS of 68 CAR-T cell naïve subjects with r/r DLBCL from study GCT3013-01 was compared to the 269 subjects treated with Breyanzi in TRANSCEND. The adjusted response rates with epcoritamab (69.1% for ORR and 43.6% for CRR) in CAR-T cell naïve subjects were comparable to those with Breyanzi (72.7% for ORR and 53.1% for CRR) (p = 0.57 and p = 0.161, respectively).

A second MAIC was conducted to assess the efficacy of epcoritamab in the 50 patients with r/r DBLCL who would be considered **CAR-T cell eligible subjects** within the subgroup of 86 CAR-T cell naïve patients from study GCT3013-01. Following adjustments of the baseline characteristics, an ESS of 44 CAR-T cell eligible subjects with DLBCL was compared to the 269 subjects in TRANSCEND. The unadjusted and adjusted ORRs with epcoritamab (72.0% and 72.3%) were comparable to Breyanzi (72.7%) (p = 0.925 and p = 0.961, respectively). The unadjusted and adjusted CRRs with epcoritamab (52.0% and 50.8%) were also comparable to Breyanzi (53.1%) (p = 0.884, and p = 0.779, respectively).

The sponsor explained that because of the timing of the enrolment into study CGT3013-01 compared with the recent approval of Breyanzi (MA: 04/04/2022), only two patients with r/r DLBCL who were treated with a CAR-T cell therapy before study entry had Breyanzi specified as their prior CAR-T cell product. Treatment with epcoritamab resulted in an ORR of 100% (2/2; 95% CI: 15.8, 100) and a CR of 50% (95% CI: 1.3, 98.7) in these two patients. The median DOR was not yet reached at the DCO.

The data presented do **not indicate an improved efficacy of epcoritamab over Breyanzi**. In addition, the efficacy observed in only two patients who were pre-treated with Breyanzi is considered too limited to conclude on a clinical meaningful benefit for those patients who have progressed or relapsed after prior treatment with Breyanzi. The sponsor should therefore provide an updated sub-analysis of all efficacy parameters measured and available to date for those patients who had progressed or relapsed after prior treatment with all the approved CAR-T cell therapies in the DLBCL cohort of study GCT3013-01. A discussion on the extrapolability of the efficacy results in patients pretreated with the other approved CAR-T cell therapies is also warranted.

Significant benefit of epcoritamab over Zynlonta based on a clinically relevant advantage

The efficacy of Zynlonta in adult patients with r/r DLBCL and HGBCL after at least two prior systemic regimens was evaluated in the pivotal, global, multicentre, open-label, single-arm phase 2 study LOTIS-2 (N=145). The sponsor claimed that epcoritamab provides a significant benefit over Zynlonta in DLBCL by providing greater efficacy and potentially fewer toxicity effects. In a naïve side-by-side comparison, epcoritamab showed numerically higher response rates and longer median DOR (including DOR of CR) compared to Zynlonta. MAIC results in patients with r/r DLBCL from study GCT3013-01 and LOTIS-2 demonstrated clinically meaningful and statistically significant improvement in efficacy with epcoritamab compared to Zynlonta.

The sponsor claimed that compared to the subjects enrolled in LOTIS-2, more patients treated with epcoritamab in study GCT3013-01 had high-risk disease characteristics. Study GCT3013-01 enrolled more subjects than LOTIS-2 who were more heavily pre-treated and had received 3 or more prior lines of therapy (68.9% vs. 56.5%). Substantially higher proportions of subjects in study GCT3013-01 had primary refractory disease (59% vs. 20%) and were refractory to their last line of therapy (82% vs. 60.7%). Additionally, study GCT3013-01 enrolled more subjects who had received prior treatment with a CAR-T cell therapy than LOTIS-2 (38.1% vs. 9%).

Despite enrolling more subjects with worse prognoses, the sponsor considered that epcoritamab demonstrated clinically meaningful deep and durable responses, characterized by substantially higher best overall- and complete response rates (61.9% ORR and 38.8% CRR) versus Zynlonta with an ORR of 48.3% and a CRR of 24.8%. After a median duration of study follow-up of 15.7 months (DCO: 30-Jun-2022), the median DOR in patients with r/r DLBCL treated with epcoritamab was 15.6 months (95% CI: 9.7, NR), whereas the median DOR in patients treated with Zynlonta was 13.4 months, after 7.8 months median duration of study follow-up (Caimi et al., 2021). The estimated number of patients remaining in response at 12 months was similar (57.2% with epcoritamab and 54.7% with Zynlonta).

The MAIC results showed that epcoritamab resulted in significantly higher response rates compared to Zynlonta in patients with r/r DLBCL. Following adjustments of the baseline characteristics, including age, sex, disease stage, primary refractory disease, prior ASCT, and prior CAR-T cell therapy, an ESS of 92 subjects with r/r DLBCL in study GCT3013-01 was identified to be comparable to the 145 subjects treated with Zynlonta in LOTIS-2. The unadjusted and adjusted ORRs were significantly higher with epcoritamab (61.9% and 65.2%, respectively) versus Zynlonta (48.3%) ($p = 0.021$ and $p = 0.009$, respectively). Similarly, the unadjusted and adjusted CRRs were significantly higher with

epcoritamab (38.3% and 38.7%, respectively) versus Zynlonta (24.1%) (p = 0.007 and p = 0.019, respectively). The survival outcomes for subjects with r/r DLBCL treated with epcoritamab showed comparable PFS and statistically significant longer median OS compared to Zynlonta, with OS HR of 0.646 for the unadjusted population (p = 0.014) and OS HR of 0.658 (p = 0.0412) for the adjusted population. The sponsor concluded that acknowledging the limitations of cross-study comparisons, these results demonstrated a clinically meaningful and statistically significant improvement in efficacy with epcoritamab compared to Zynlonta.

The unanchored MAIC approach conducted led to a down-weighting of 33.8% (92/139) of the r/r DLBCL patients in study GCT3013-01 for the adjusted population compared to the DLBCL population from LOTIS-2. This extend of ESS reduction is considered acceptable with regards to the robustness and reliability of the data presented, and consequently the interpretability of the MAIC results.

The sponsor also claimed significant benefit of epcoritamab over Zynlonta with regards to patient tolerability and treatment continuity. However, given the limited experience with epcoritamab from a small single-arm study with limited follow-up, the claim of improved safety in comparison to Zynlonta cannot be concluded on at present stage and no adequate quantification is possible for the descriptive cross-study comparison presented.

The indirect treatment comparisons of the efficacy results from the pivotal study LOTIS-2 for Zynlonta versus that reported for epcoritamab in study GCT3013-01 provided sufficient evidence to **support the claim of a clinically relevant advantage based on improved efficacy** in terms of higher and sustained ORR and CRR with epcoritamab compared to that obtained with Zynlonta in patients with r/r DLBCL in the third- and later lines setting.

Significant benefit based on a major contribution to patient care

The sponsor also claimed that epcoritamab offers a significant benefit to patients with r/r DLBCL by providing a major contribution to patient care by being administered SC, whereas the satisfactory methods of treatment are typically administered as IV infusions or injections. Compared to IV administration, SC administration of oncology medicines has been shown to reduce treatment burden to the patients and lower drug administration time for the medical staff and patients (Ponzettin 2016 and Harvey 2022).

Patient satisfaction on the SC route of administration for epcoritamab was assessed during a qualitative subject experience interview. Of the 20 subjects from study GCT3013-01 participated in the interview, 16 (80%) were from the LBCL cohort. The participating subjects were from France (55%), the UK (20%), and the US (25%). Seventy percent (14/20) of subjects were interviewed after their Cycle 10 visit, and 30% (6/20) of subjects had terminated early. Proportion of males and females were equal, and the mean age of subjects was 66 years (range: 21-84). The majority of subjects (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 subjects reported a preference to receiving treatment by injection under the skin over the IV mode of administration. However, a significant limitation of these results is that the interviews were conducted with patients from a single-arm study and there is therefore no other treatment to compare the reported findings with. The results cannot therefore be considered robust and conclusive evidence of a major contribution to patient care.

In conclusion, the claim of significant benefit for epcoritamab over Kymriah and Zynlonta for the target patient population can be considered established based on the data provided from their pivotal studies.

However, the sponsor has not provided sufficient evidence to demonstrate significant benefit compared to Yescarta and Breyanzi in adult patients with r/r DLBCL in the third- and later lines setting. The sponsor was therefore requested to further discuss the arguments for significant benefit over these two products for the target patient population and based on supplementary data.

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

Of note: The sponsor submitted clinical data to support a claim of significant benefit in terms of improved efficacy of epcoritamab over glofitamab in DLBCL patients. However, these data will not be discussed in this report as the decision from the EC on marketing authorisation has not yet been published in the official journal and can therefore not be considered a satisfactory method.

The sponsor further justified the claim for significant benefit of epcoritamab over axi-cel (Yescarta) and liso-cel (Breyanzi) in the third- and later lines setting for the target DLBCL population based on more mature efficacy data from study GCT3013-01 as requested.

Efficacy in patients previously treated with CD19-directed CAR-T cell therapy by compound

The sponsor provided updated efficacy results with epcoritamab in patients with r/r DLBCL from study GCT3013-01 based on a more recent DCO date of 18-Nov-2022 with around 5 months extended study follow-up. A summary of the efficacy observed in patients from study GCT3013-01 who were treated with epcoritamab after prior CAR-T cell therapy based on the latest DCO is presented in Table 4.

Among the 53 patients who had received CAR-T cell therapy as prior treatment in study GCT3013-01, most were treated with either Kymriah (n=22) or Yescarta (n=21), whereas 2 patients were treated with Breyanzi, and the remaining 8 patients had received a CAR-T cell therapy that was not specified or was an investigational CAR-T therapy. In the 53 patients who had received prior CAR-T cell therapy in the DLBCL cohort of study GCT3013-01, epcoritamab resulted in an ORR of 52.8% (95% CI: 38.6, 66.7) and a CRR of 35.8% (95% CI: 23.1, 50.2), which were somewhat lower, but still consistent with the responses reported for the overall DLBCL cohort (ORR: 61.9% [95% CI: 53.3, 70.0], CRR: 38.8% [95% CI: 30.7, 47.5]). The median DOR among the responders was not reached (95% CI: 5.4. NR).

In the 22 patients who had previously been treated with Kymriah, epcoritamab resulted in an ORR of 59.1% (95% CI: 36.4, 79.3) and a CRR 45.5% (95% CI: 24.4, 67.8), which were consistent with the responses reported for the overall DLBCL cohort of study GCT3013-01. At a median follow-up of 15.2 months among the responders to epcoritamab who had received prior Kymriah, the median DOR and DOCR were still not reached. The estimated 12-month rate for DOR was 76.9% and 100% for DOCR.

In the 21 patients who had previously been treated with Yescarta, epcoritamab resulted in an ORR of 38.1% (95% CI: 18.1, 61.6) and a CRR of 19.0% (95% CI: 5.4, 41.9). At a median follow-up of 19.6 months among the responders to epcoritamab who had received prior Yescarta, the median DOR was 7.6 months (95% CI: 0.8, NR) and the median DOCR was still not reached (95% CI: 9.7, NR). The estimated 12-month rate for DOR was 37.5% and 75% for DOCR. As already mentioned above, the efficacy observed in these patients was generally lower than the results reported in the overall DLBCL cohort and there is uncertainty in the point estimates for the observed responses as indicated by their wide 95% CIs.

Table 3. Response outcomes of epcoritamab in patients with r/r DLBCL who had previously received CAR-T cell therapy in study GCT3013-01 (DCO: 18-Nov-2022)

	All subjects with prior CAR-T therapy	Type of CAR-T Therapy			
		Yescarta	Kymriah	Breyanzi	Not Specified
N	53	21	22	2	8
Best response					
Overall response rate, % [95% CI][a, b]	52.8 [38.6,66.7]	38.1 [18.1, 61,1]	59.1 [36.4. 79.3]	100 [15.8, 100}	62.5 [24.5, 91.5]
Complete response rate, % [95% CI][c]	35.8 [23.1, 50.2]	19.0 [5.4, 41.9]	45.5 [24.4, 67.8]	50 [1.3, 98.7]	50 [15.7, 84.3]
Duration of response					
Median, in months [95 CI%][d]	NR [5.4. NR]	7.6 [0.8, NR]	NR [2.8, NR]	NR [2.6, NR]	NR [1.4, NR]
Median follow-up, in months [95% CI][e]	15.2 [13.1, 16.3]	19.6 [19.2, NR]	15.2 [4.4, 16.1]	8.3 [2.6, NR]	4.4 [1.4, NR]
Percentage of Subjects remaining in Response [95% CI]					
6-month [95 CI%]	69.7 [48.1, 83.7]	50.0 [15.2, 77.5]	76.9 [44.2, 91.9]	100.0 [100.0, 100.0]	75.0 [12.8, 96.1]
9-month [95 CI%]	65.1 [43.1, 80.3]	50.0 [15.2, 77.5%]	76.9 [44.2, 91.9]	0.0 [NR, NR]	75.0 [12.8, 96.1]
12-month [95 CI%]	60.4 [38.4, 76.7]	37.5 [8.7, 67.4]	76.9 [44.2, 91.9]		75.0 [12.8, 96.1]
Median, in months [95 CI%][e]	NR [15.3, NR]	NR [9.7, NR]	NR [15.3, NR]	NR [NR, NR]	NR [1.4, NR]
Median follow-up, in months [95% CI][d]	15.2 [4.4, 16.3]	19.6 [19.2, NR]	15.2 [4.4, 16.1]	2.6 [NR, NR]	4.4 [1.4, NR]
Percentage of Subjects with CR remaining in Response [95% CI]					
6-month [95 CI%]	100.0 [100.0, 100.0]	100 [15.2, 77.5]	100 [100, 100]		100 [100, 100]
9-month [95 CI%]	100.0 [100.0, 100.0]	100 [15.2, 77.5]	100 [100, 100]		100 [100, 100]
12-month [95 CI%]	92.9 [59.1, 99.0]	75.0 [12.8, 96.1]	100 [100, 100]		100 [100, 100]

CI = confidence interval; DLBCL = diffuse large B-cell lymphoma; NE = not evaluable; NL = not listed; NR = not reached; OS = overall survival; PFS = progression-free response; PR = partial response.

a. From the updated analysis of 139 subjects with DLBCL from the pivotal aNHL expansion cohort (n=157) of GCT3013-01 trial (clinical DCO: 18 Nov 2022) Responses were based on ORR and CR, as determined by IRC, Lugano response criteria (Cheson 2014). Source: t14.2_1.1.1.1Q1 to t14.2_1.1.1.6Q1 and t14.2_1.7.1.1.1Q1 to t14.2_1.7.1.6.Q1,
b. ORR = CR + PR
c. Based on the Clopper and Pearson method
d. Based on Kaplan Meier estimate
e. Based on reverse Kaplan-Meier estimate. Additionally, we have made further observations to address the agency comments regarding prior ITT

The efficacy results for epcoritamab in the two patients who had previously been treated with Breyanzi was also the same as reported at an earlier DCO date with an ORR of 100% (95% CI: 15.8, 100) and a

CRR of 50% (95% CI: 1.3, 98.7). At a median follow-up of 8.3 months, the median DOR had not been reached (95% CI: 2.6, NR), and the 6-month percentage of patients remaining in response was 100%.

The sponsor considered that clinical meaningful and durable responses were observed across all the prior CAR-T cell subgroups presented and concluded that epcoritamab is offering a clinical benefit for patients with r/r DLBCL who were previously treated with either Kymriah, Yescarta, or Breyanzi and had progressive or relapsed disease.

The sponsor also argued that a comparison of the efficacy outcomes reported between the CAR-T cell naïve DLBCL subgroup treated with epcoritamab in study GCT3013-01 and the ITT populations treated with the individual CAR-T cell products in their pivotal studies demonstrated that epcoritamab showed higher than or similar efficacy to these products. Patients who were treated with epcoritamab in this subgroup (n=86) achieved an ORR of 67.4% and a CRR of 41.9%, whereas the ORRs and CRRs were correspondingly 36.7% and 27.9% for Kymriah (n=167; Novartis Europharm 2018), 66% and 47% for Yescarta (n=111; Kite Pharma 2018), and 60.1% and 43.0% for Breyanzi (n=298; Celgene 2022).

Furthermore, epcoritamab is administered SC, whereas the approved CAR-T cell therapies require infusion, as well as additional hospitalization for weeks after CAR-T cell administration. Additional considerations include issues such as patients with rapidly evolving disease being unable to await manufacturing of CAR-T cell therapy and the requirement for specialized care.

The sponsor claimed that given the longer follow-up with larger subsets of patients who were previously treated with Yescarta and Kymriah, durable responses observed with epcoritamab after receiving these two CAR-T cell therapies may be extrapolated to those pre-treated with Breyanzi for several reasons. Importantly, the mechanism of resistance leading to eventual disease relapse from all three CAR-T cell therapies are similar:

a. All three approved CAR-T cell therapies for DLBCL are CD19-directed genetically modified autologous T-cell immunotherapy. CAR-T cell resistance is likely driven by CD19 antigen escape, whereby tumours turn CD19-negative (Majzner and Mackall, 2018). Epcoritamab targets a different antigen epitope, CD20, and therefore will remain active in those patients previously treated with Breyanzi or the other two CAR-T cell therapies who have developed this resistance mechanism.

b. Early CAR-T cell exhaustion (Haradhvala et al., 2022) and an increase in "CAR-T regulatory cells" (Good et al., 2022) are associated with CAR-T cell treatment failure. Epcoritamab relies on naive T-cells for tumour cell killing, thereby overcoming this intrinsic CAR-T cell resistance mechanism shared across all three approved CAR-T cell therapies. Epcoritamab activity is consequently expected to be similar in patients pre-treated with Breyanzi as those pre-treated with the two other approved CAR-T cell products.

The COMP agreed that the updated efficacy analysis in the subset of patients with prior CAR-T cell therapy in the DLBCL cohort of study GCT3013-01 confirmed that epcoritamab offered a clinical meaningful benefit for those patients who have progressed or relapsed after prior treatment with Yescarta, in addition to Kymriah, as they achieved sustained ORRs to epcoritamab. The responses observed in these patient subgroups could therefore be considered to constitute a clinically relevant advantage for patients with r/r DLBCL in the third- and later lines setting although the data on the time-dependent endpoints were still immature.

Because of the timing of the enrolment into study GCT3013-01 and the recent approval of Breyanzi, only two patients with r/r DLBCL who were treated with a CAR-T cell therapy before study entry had

Breyanzi specified as their prior CAR-T cell product. Both patients responded to epcoritamab, but due to the limited number of patients it is impossible to draw conclusions about the effect in those who have previously been treated with Breyanzi. Nevertheless, the durable responses to epcoritamab observed in the 53 patients who had received CAR-T cell therapy as prior treatment before study entry, which represented over one third (38.1%; 53/139) of the overall DLBCL population in study GCT3013-01, were considered as a clinically meaningful benefit of epcoritamab in these patients.

The COMP considered that the sustained ORR observed in the relatively large number of patients treated with epcoritamab who were pre-treated with at least two of the approved CD19-directed CAR-T cell products in the DLBCL cohort of study GCT3013-01 combined with the lack of a scientific rationale that efficacy post Breyanzi would differ from that observed after prior treatment with Kymriah, since both CAR constructs include the same costimulatory endodomain derived from the 4-1BB molecule (CD137) in addition to targeting the same antigen, suggesting that the benefit of epcoritamab observed in the subgroup of patients who have progressed or relapsed after prior treatment with Kymriah can be extrapolated to patients who have failed previous treatment with Breyanzi. The significant benefit of epcoritamab over Breyanzi in addition to Kymriah and Yescarta can therefore be considered justified based on a clinically relevant advantage for patients with r/r DLBCL who have progressed or relapsed after previous treatment with the authorised CD19-directed CAR-T cell products in the third- and later lines setting.

In conclusion, the claim of significant benefit of epcoritamab compared to the approved CAR-T cell products tisa-cel (Kymriah), axi-cel (Yescarta), and liso-cel (Breyanzi), and loncastuximab tesirine (Zynlonta) for adult patients with r/r DLBCL in the third- and later lines setting can be considered established based on the data provided from their pivotal studies.

4. COMP position adopted on 21 July 2023

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan condition of the designated Orphan Medicinal Product;
- the prevalence of diffuse large B-cell lymphoma (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be 4.3 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is chronically debilitating due to constitutional symptoms, local symptoms of lymphadenopathy, end-organ damage from disease involvement, and bone marrow failure that may lead to infections, anaemia, and thrombocytopenia and life-threatening in patients not responding to treatment;
- although satisfactory methods for the treatment of the condition have been authorised in the European Union for all patients covered by Tepkinly, the assumption that Tepkinly may be of potential significant benefit to those affected by the orphan condition still holds. The sponsor has provided clinical study data that demonstrated improved and sustained response rates with Tepkinly as compared to Zynlonta and a clinically meaningful benefit in subgroups of patients who have progressed or relapsed after prior treatment with the authorised CAR-T cell products (Kymriah, Yescarta, and Breyanzi) for adult patients with relapsed or refractory diffuse large B-cell lymphoma after two or more lines of systemic therapy.

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The Committee for Orphan Medicinal Products has recommended that Tepkinly, epcoritamab, for treatment of diffuse large B-cell lymphoma (EU/3/22/2581) is not removed from the Community Register of Orphan Medicinal Products.