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Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Columvi (glofitamab)
Treatment of diffuse large B-cell lymphoma
EU/3/21/2497

Sponsor: Roche Registration GmbH

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	Glofitamab
Other name(s)	--
International Non-Proprietary Name	Glofitamab
Tradename	Columvi
Orphan condition	Treatment of diffuse large B-cell lymphoma
Sponsor's details:	Roche Registration GmbH Emil-Barell-Strasse 1 Grenzach 79639 Grenzach-Wyhlen Baden-Wuerttemberg Germany
Orphan medicinal product designation procedural history	
Sponsor/applicant	Roche Registration GmbH
COMP opinion	9 September 2021
EC decision	15 October 2021
EC registration number	EU/3/21/2497
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Aaron Sosa Mejia / Jan Mueller-Berghaus
Applicant	Roche Registration GmbH
Application submission	25 March 2022
Procedure start	19 May 2022
Procedure number	EMA/H/C/005751
Invented name	Columvi
Proposed therapeutic indication	Columvi 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 Columvi can be found in the European public assessment report (EPAR) on the Agency's website ema.europa.eu/en/medicines/human/EPAR/columvi
CHMP opinion	26 April 2023
COMP review of orphan medicinal product designation procedural history	
COMP rapporteurs	Frauke Naumann-Winter / Maria Elisabeth Kalland
Sponsor's report submission	18 August 2022, 15 December 2022 and 24 March 2023
COMP discussion and adoption of list of questions	18-20 April 2023
Oral explanation	16 May 2023
COMP opinion	17 May 2023

2. Grounds for the COMP opinion

The COMP opinion that was the basis for the initial orphan medicinal product in designation in 2021 was based on the following grounds:

- the intention to treat the condition with the medicinal product containing glofitamab was considered justified based on preliminary clinical data from patients with relapsed and refractory diffuse large B-cell lymphoma who respond to treatment with glofitamab;
- the condition is chronically debilitating due to involvement of single or multiple nodal or extranodal sites, including the gastrointestinal tract and bone marrow and life-threatening in patients not responding to first-line treatment;
- the condition was estimated to be affecting approximately 4 in 10,000 persons in the European Union, at the time the application was made.

Thus, the requirements under Article 3(1)(a) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled.

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 glofitamab will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data in patients affected by the condition who had relapsed or did not respond to at least two prior systemic treatments. These patients showed clinically relevant responses when treated with the product. 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 glofitamab as an orphan medicinal product for the orphan condition: treatment of diffuse large B-cell lymphoma."

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 an aggressive B-cell lymphoma histologically characterised by dense proliferation of neoplastic B-cells. It represents the most common histological subtype of non-Hodgkin lymphomas (NHL), 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). DLBCL accounts for 25% to 45% of all NHL cases worldwide (Wild et al, 2020), and although it can occur at

any age, it typically affects older individuals (median age at presentation is >65 years), and it is slightly more frequent in males (Mounier et al, 2015).

In recognition of the unique clinical and pathological features of DLBCL subtypes and associated therapeutic implications, the World Health Organization (WHO) updated the previous 2008 classification of lymphoid neoplasms in 2016 and also 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).

The approved therapeutic indication "Columvi 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 is confirmed by the positive benefit/risk assessment of the CHMP, see EPAR.

Chronically debilitating and/or life-threatening nature

The sponsor briefly outlines the chronically debilitating and life-threatening nature of the disease and refers to it as having an aggressive natural history, with a median survival of less than one year if left untreated (Koff, 2017). The clinical course of DLBCL can be debilitating due to constitutional symptoms, local symptoms of lymphadenopathy and bone marrow failure that may lead to infections, anaemia, and thrombocytopenia.

The sponsor has not identified any significant changes in the seriousness of DLBCL since the orphan designation was granted in 2021. The COMP agreed that the condition remains 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 with relapsed/refractory disease who do not respond to treatment.

Number of people affected or at risk

The sponsor proposed a prevalence of 4.28 per 10,000 persons.

The sponsor has identified additional and updated sources as compared to the orphan designation application in 2021. Estimates were updated for NORDCAN, IKNL (The Netherlands), Slovenian Cancer Registry, and Germany. Additionally, new sources of estimates from Spain (REDECAN) and Belgium were identified. The average complete/lifetime prevalence (population-weighted using data from Slovenia, Italy, Germany, and Spain) was estimated to be 7.54 [min–max: 4.93 to 7.73]. To reflect patients who would be considered in the non-cured pool (i.e. due to diagnosis, treatment as new case or relapsed, and various modes of monitoring) the sponsor proposes to use a 10-year limited duration estimate. An updated 10-year limited-duration prevalence that was population-weighted and is based on population-based registry data (using data from NORDCAN, The Netherlands, Slovenia, Germany, Belgium) is estimated at 4.28 per 10,000. For the sensitivity analysis, an updated modelled prevalence (incidence-based cohort model years 2012 to 2021) of the noncured DLBCL pool yielded a prevalence of 4.81 per 10,000.

Table 1. DLBCL Prevalence (per 10,000) Based on Estimates Extracted from Population-Based Cancer Registry Sources in the EU27, UK, and USA

Cancer Registry	Country/ies	Year (latest)	Population	Prevalence Period Capture			
				5 years	10 years	20 years	Complete / lifetime
NORDCAN[a]	Denmark, Faroe Islands, Finland, Greenland, Iceland, Norway, Sweden	2019	27,036,000	2.60	4.33	6.88	-
IKNL[b]	The Netherlands	2021	17,172,569	3.09	5.12	7.11	-
Slovenia Cancer Registry[c]	Slovenia	2018	2,077,837	1.99	3.26	-	4.93
AIRTUM[d]	Italy	2020	60,731,000	-	-	-	7.73
Robert Koch Institute[e]	Germany	2018	82,349,000	2.90	4.78	6.94	7.45
REDECAN[f]	Spain	2020	46,445,000	2.33	-	-	7.55
Belgium Cancer Registry[g]	Belgium	2018	11,430,000	2.34	3.93	-	-
HMRN	United Kingdom	2016	65,610,000	2.63	4.23	-	-
SEER[h]	USA	2018	326,800,000	2.40	3.99	5.74	6.16
EU27 estimate[i]		2022		2.54	**4.28**	6.98	6.92

AIRTUM=Associazione Italiana dei Registri Tumori (Italian Association of Cancer Registries); DLBCL=diffuse large B-cell lymphoma; EU=European Union; HMRN=Haematological Malignancy Research Network; IKNL=Integraal Kankercentrum Nederland (Comprehensive Cancer Center of the Netherlands); NHL=non Hodgkin's lymphoma; NORDCAN=Association of the Nordic Cancer Registries; REDECAN=Red Espanola de Registros de Cancer (Spanish Network of Cancer Registries); SEER=Surveillance, Epidemiology, and End Results.
a Based on pooled cancer registry data from seven Nordic countries: Denmark, Faroe Islands, Finland, Greenland, Iceland, Norway, Sweden for 2019 and applying EU weighted-average ratio of DLBCL to NHL (35.02%) to the gender-specific prevalence proportions for 2019.
b Based on extracting the total counted prevalence cases for 2021 for the duration of interest (5 year=5313, 10 year=8798, 20 year=12217), divided by the 2021 population in The Netherlands.
c Based on extracting the total counted NHL prevalence cases for 2018 for the duration of interest (5 year=414, 10 year=678, lifetime=1026), multiplied by DLBCL to NHL incidence rate ratio for Slovenia in 2018 (29.6%), divided by the 2018 population in Slovenia.
d Based on the number of DLBCL cases reported (n=46751) divided by the 2020 population in the AIRTUM registry report for 2020.
e Based on applying the German 2018 DLBCL to NHL ratio (37% in 2018) to the total NHL reported prevalence cases in 2018 for each period of capture. Complete/lifetime prevalence is reported as 25 years.
f Based on applying the Spanish 2015 DLBCL to NHL ratio (35.5%) to the total NHL-reported prevalence cases in 2020 at 5 years (n=31,052) and lifetime (n=100,058).
g Based on extracting the total counted prevalence cases for 2018 for the duration of interest (5 year=1762, 10 year=3086), divided by the 2020 population in Belgium.
h SEER registry calculates the complete prevalence using 26-year period up to year 2018.

I The EU27 estimate for the year 2022 is based on the latest observed data. Each prevalence estimate for the EU27 is an average based on population-based registry data available.

The COMP agreed with the sponsor's proposal and concluded that the prevalence is 4.3 in 10,000 persons in the European community based on most recent publications and updated registries.

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 referred to the European Society for Medical Oncology (ESMO) clinical practice guidelines for diagnosis, treatment, and follow-up for DLBCL, which describe some of the treatment strategies available to these patients in the first- and second line setting (Tilly et al., 2015). They recognised that the treatment landscape has evolved since the ESMO guidelines became publicly available, as new medicinal products such as the three approved CAR-T-cell therapies tisagenlecleucel (hereinafter referred to as tisa-cel; Kymriah), axicabtagene ciloleucel (hereinafter referred to as axi-cel; Yescarta), and lisocabtagene maraleucel (hereinafter referred to as liso-cel; Breyanzi), polatuzumab vedotin (Polivy), tafasitamab (Minjuvi), and loncastuximab tesirine (Zynlonta) have been authorised in the EU after 2015. These products are therefore not included in the current ESMO guidelines.

R-CHOP given in 21-day intervals remains the standard of care therapy for patients with previously untreated DLBCL, although Polivy+R-CHP was recently approved in the EU as first-line therapy after showing meaningful benefit over R-CHOP in a Phase 3 randomized clinical trial (Polivy MA extension: 24/05/2022, Procedure No. EMEA/H/C/004870/II/0012).

The sponsor provided a detailed table outlining all existing methods for the treatment of patients with DLBCL in the European community, and centrally as well as nationally approved products.

Table 2. Currently Available Treatment Options Based on Line of Therapy

Patient segment	**1L**	**2L**	**3L and beyond**
All patients	R-CHOP or R-CHOP-like regimens Polivy+R-CHP		
Transplant-eligible		Salvage chemotherapy (R-DHAP/ICE/GDP) + HDCT + ASCT*	
		Allogeneic transplant	
Transplant-ineligible		Platinum-based and/or gemcitabine-based regimens (R-GemOx) Polivy + BR, bendamustine-rituximab Minjuvi + lenalidomide	
Relapsed <12 months or primary refractory disease		Yescarta	
All patients			CAR T-cell therapy Zynlonta Pixuvri#
			Clinical trials (new MoAs)

ASCT=autologous stem cell transplant; BR=bendamustine+rituximab; CAR=chimeric antigen receptor; HDCT=high dose chemotherapy; MoA=mechanism of action; R-CHOP=rituximab+cyclophosphamide, doxorubicin, vincristine, and prednisone; R-DHAP=rituximab+dexamethasone, cytarabin, cisplatin; R-GDP=rituximab+gemcitabine, cisplatin, dexamethasone; R-ICE=rituximab+ifosfamide, carboplatin, etoposide.
* NCCN and ESMO guidelines suggest patients who relapse after 2L therapy are unlikely to respond to subsequent therapy and therefore generally are not eligible for ASCT.
\# Benefit of Pixuvri has not been established in 5L+ for patients refractory to last therapy.

They also summarised the medicinal products authorised for the treatment of r/r DLBCL or for the broader indication of r/r aggressive NHL in the third- and later lines setting in the 27 EU member states (EU27) and European Economic Area (EEA), and specified whether these products were considered relevant for a discussion on the significant benefit of Columvi in DLBCL.

Table 3. Medicinal Products Authorized for the Treatment of 3L+ r/r DLBCL in the EU

Product (INN)	**Indication per SmPC**	**Satisfactory method**
Yescarta (axicabtagene ciloleucel)	Yescarta is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and primary mediastinal large B-cell lymphoma (PMBCL), after two or more lines of systemic therapy.	Satisfactory as there is a complete overlap with the proposed therapeutic indication of glofitamab
Kymriah (tisagenlecleucel)	Kymriah 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.	Satisfactory as there is a complete overlap with the proposed therapeutic indication of glofitamab

Product (INN)	Indication per SmPC	Satisfactory method
Breyanzi (lisocabtagene maraleucel)	Breyanzi is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), primary mediastinal large B-cell lymphoma (PMBCL) and follicular lymphoma grade 3B (FL3B), after two or more lines of systemic therapy.	Satisfactory as there is a complete overlap with the proposed therapeutic indication of glofitamab
Zynlonta (loncastuximab tesirine)	Zynlonta as monotherapy is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and high-grade B-cell lymphoma (HGBL), after two or more lines of systemic therapy.	Satisfactory as there is a complete overlap with the proposed therapeutic indication of glofitamab
Polivy (polatuzumab vedotin)	Polivy in combination with bendamustine and rituximab is indicated for the treatment of adult patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL) who are not candidates for haematopoietic stem cell transplant.	Non satisfactory because the indication is restricted to patients who are not candidates for HSCT and can be used in second line
Minjuvi (tafasitamab)	Minjuvi is indicated in combination with lenalidomide followed by Minjuvi monotherapy for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) who are not eligible for autologous stem cell transplant (ASCT).	Non satisfactory because the indication is restricted to patients who are not candidates for ASCT and can be used in second line
Pixuvri (pixantrone)	Pixuvri is indicated as monotherapy for the treatment of adult patients with multiply relapsed or refractory aggressive Non-Hodgkin B-cell Lymphomas (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.	Non satisfactory because it is not indicated in fifth and later lines

Proposed therapeutic indication for glofitamab: Glofitamab as monotherapy is indicated for the treatment of adult patients with r/r DLBCL, after two or more lines of systemic therapy.

Very recently, in December 2022, loncastuximab tesirine (Zynlonta) was conditionally approved as "monotherapy is indicated for the treatment of adult patients with relapsed or refractory (r/r) DLBCL and high-grade B-cell lymphoma (HGBL), after two or more lines of systemic therapy". This therapeutic indication overlaps with the one intended for glofitamab and Zynlonta is therefore considered a satisfactory method for the target patient population of glofitamab for the purpose of orphan designation.

Pixuvri (pixantrone) 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. Although glofitamab is to be used in r/r DLBCL, the therapeutic indications are not considered to be completely overlapping since glofitamab is intended to be used in the third and later lines while Pixuvri is limited to third and fourth lines.

Polivy (polatuzumab vedotinin) in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone (R-CHP) is indicated for the treatment of adult patients with previously untreated DLBCL, and in combination with bendamustine and rituximab for the treatment of adult patients with r/r DLBCL who are not candidates for haematopoietic stem cell transplant (HSCT). As Polivy should be used only in r/r DLBCL patients who are not candidates for HSCT, the therapeutic indications of Polivy and glofitamab are not considered to be completely overlapping.

Minjuvi (tafasitamab) is indicated in combination with lenalidomide followed by Minjuvi monotherapy for the treatment of adult patients with r/r DLBCL who are not eligible for ASCT. As Minjuvi should be used only in r/r DLBCL patients who are not candidates for HSCT, the therapeutic indications of Minjuvi and glofitamab are not considered to be completely overlapping.

Therefore, Pixuvri, Polivy and Minjuvi are not considered satisfactory methods for the entire patient population covered by the proposed indication for glofitamab and will not be discussed under the significant benefit section.

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 glofitamab and will be further discussed below.

Significant benefit

The sponsor did not seek any protocol assistance from EMA to agree on the approach for collecting the evidence needed for the justification of significant benefit of glofitamab over existing methods of treatment for patients with r/r DLBCL who have received at least two prior lines of systemic therapy.

The sponsor argued that glofitamab is of significant benefit over the CAR-T cell therapies based on a clinically relevant advantage in terms of improved efficacy and a better safety profile in comparison to the approved CAR-T cell products and loncastuximab tesirine (Zynlonta) for r/r DLBCL patients in the third- and later lines setting. It was also claimed that glofitamab provides a clinically relevant advantage to patients who have failed prior treatment with several CAR-T cell products, and a major contribution to patient care based on immediate availability for treatment planning and less restrictions on daily living after treatment. Each claim will be discussed separately below.

The sponsor presented data from an expanded efficacy population from study NP30179, which is an ongoing multicenter, multicohort, open-label, dose-escalation and dose-expansion first-in-human (FIH), single-arm phase 1/2 study used to obtain the pivotal evidence for glofitamab in patients with r/r DLBCL after two or more lines of systemic therapy in the conditional MA application. The study was designed to evaluate the safety, efficacy, tolerability, and pharmacokinetics of glofitamab administered by intravenous (IV) infusion as a single agent and in combination with obinutuzumab following pre-treatment with a fixed dose of 1000 mg obinutuzumab (Gazyvaro) in patients with r/r NHL. The expanded efficacy population included 149 patients with r/r DLBCL not otherwise specified (NOS; n=110 [74%]), transformed follicular lymphoma (trFL; n=29 [20%]), and HGBCL (n=10 [7%]) who had received at least two prior lines and were treated with glofitamab step-up dosing of 2.5/10/30 mg pooled from the cohorts D2[Sub. 2], D3, and D5. The sponsor argued that this pooled efficacy

population aligns more closely with the primary safety population (N=154, including patients with primary mediastinal B-cell lymphoma [PMBCL]). The data cut-off (DCO) date for the efficacy and safety analyses provided was 15-Jun-2022.

The primary efficacy objective of the phase 2 part is to evaluate the antitumor activity of glofitamab as a single agent following obinutuzumab in patients diagnosed with DLBCL as measured by independent review committee (IRC) assessed complete response (CR) rate according to the Lugano classification criteria (Cheson et al., 2014). Secondary efficacy outcome measures included IRC-assessed overall response rate (ORR), duration of complete response (DOCR), duration of response (DOR), time to first complete response (TFCR), time to first overall response (TFOR), and progression-free survival (PFS).

The median number of prior cancer therapies in the pooled population was 3 (range: 2–7). Overall, 60% of the patients had received 3 or more prior lines of systemic therapy. All patients had received prior chemotherapy, anti-CD20 monoclonal therapy, and alkylator therapy, and 33% (49/149) of the patients had received prior CAR-T cell therapy. The median time from last prior therapy to start of study treatment was 2.7 months. The majority of patients (89%) were refractory to any prior therapy, with 58% refractory to first-line therapy and 84% refractory to their last prior therapy. Overall, 83% of the patients were refractory to any prior anti-CD20 therapy. The majority of patients who received prior CAR-T cell therapy were refractory to it (44/49 [90%]).

Key results in the efficacy populations are summarized in Table 4. Median duration of follow-up at the DCO was 13.4 months (95% CI: 8.9, 15.2) in the pooled efficacy population.

Table 4. Updated Efficacy (per IRC) in patients with r/r DLBCL NOS, trFL, and HGBCL ≥ 2 prior lines (DCO: 15 June 2022)

	Glofitamab 2.5/10/30 mg		**Glofitamab ≥ 10 mg**
	Cohort D3 N=102	**Cohorts D2 [Sub 2], D3, D5 N=149**	**Doses ≥ 10 mg N=97**
Primary Efficacy Measure	**IRC-Assessed Complete Response Rate**		
n, IRC-CR[a]	35	59	35
IRC-CR Rate (%) [95% CI]	34 [25, 44]	40 [32, 48]	36 [27, 46]
Secondary Efficacy Measures	**IRC-Assessed Overall Response Rate**		
n, IRC-OR (CR+PR)[a]	50	76	48
IRC-OR Rate (%) [95% CI]	49 [39, 59]	51 [43, 59]	50 [39, 60]
	Duration of IRC-Complete Response (DOCR)		
Complete responders without subsequent event at CCOD	26/35 (74%)	45/59 (76%)	22/35 (63%)
Median DOCR[a] (months) [95% CI]	NE [18.4, NE]	NE [16.8, NE]	NE [17.9, NE]
	Duration of IRC-Overall Response (DOR)		
Responders without subsequent event at CCOD	28/50 (56%)	48/76 (63%)	27/48 (56%)
Median DOR[a] (months) [95% CI]	14.4 [8.6, NE]	16.8 [11.4, NE]	24.7 [9.4, NE]

CCOD=clinical cutoff date; CI=confidence interval; CR=complete response; IRC=Independent Review Committee; NE=not evaluable; PR=partial response.
Median duration of follow up at 15 June 2022 CCOD: 15.0 months (Cohort D3), 13.4 months (Cohorts D2 [Sub. 2], D3, and D5 pooled), and 26.0 months (doses > 10 mg).
a Lugano classification (Cheson et al. 2014).

Significant benefit of glofitamab versus the approved CAR-T cell products

Comparable efficacy in a more heavily pre-treated population:

The sponsor starts out by descriptively comparing the results of the pivotal studies for the CAR-T cell products and glofitamab (Table 4). The sponsor considers that the patient population in study NP30179 represents a harder to treat population than those included in the pivotal studies for the approved CAR- T cell products:

- Patients receiving glofitamab were slightly older (median age 66 years) than patients enrolled to receive Yescarta, Kymriah, and Breyanzi in the pivotal studies (median age 58-62 years).
- Patients in study NP30179 were more heavily pre-treated as the pivotal CAR-T cell studies included patients pre-treated with 1 or more prior lines of therapy.
- Patients in glofitamab study NP30179 were more refractory to their prior therapies than those included in the pivotal studies for Yescarta and Kymriah.
- A substantial proportion (33%; 49/149) of patients receiving glofitamab had received CAR-T cell therapy in a prior line. The majority (36/49 patients [73%]) received CAR-T cell therapy in the most recent line, and the majority (44/49 patients [90%]) were refractory.

The sponsor claimed that the response rates and durations of response observed with glofitamab are broadly comparable to those reported for the approved CAR-T cell products, despite being studied in a more difficult to treat patient population (Table 5). In particular, the IRC-assessed CR rate of 40% (95% CI: 32, 48) for glofitamab in the pooled efficacy population (excluding patients with PMBCL) is in the same range as those reported for the intent-to-treat (ITT) populations of the CAR-T cell therapies (CRR: 28-47%).

Table 5. Efficacy of glofitamab compared with CAR-T cell therapies indicated for 3L+ r/r DLBCL (DCO: 15-Jun-2022)

Therapy / N, Efficacy	**YESCARTA[a]** **(DLBCL, PMBCL)** **N=101 (infused), N=111 (enrolled)**	**KYMRIAH[b]** **(DLBCL)** **N=115 (infused), N=167 (enrolled)**	**BREYANZI[c]** **(DLBCL, PMBCL)** **N=298 (enrolled)**	**Glofitamab** **(DLBCL, PMBCL)** **N=108 (Cohort D3), N=155 (Cohorts D2 [Sub 2], D3, D5)**	**Glofitamab** **(DLBCL)** **N=102 (Cohort D3), N=149 (Cohorts D2 [Sub 2], D3, D5)**
Age [years], median (range)	58 (23-76)	58 (22-74) (ITT)	62 (18-82)	66 (21-90), 66 (21-90)	66.5 (21-90), 67 (21-90)
Age ≥ 65 years	24%	28.1%	38.9%	54%, 54%	56%, 56%
Prior therapies, median (range)	3 (1-10)	3 (1-6)	3 (1-12)	3 (2-7), 3 (2-7)	3 (2-7), 3 (2-7)
Refractory status:					
Last therapy	77%	59% (ITT)	83%[d]	83%, 85%	82%, 84%

Primary refractory	26%[e]	not reported	53%[f]	60%, 58%	60%, 58%
Refractory to CAR-T	not applicable	not applicable	not applicable	32%, 30%	31%, 30%
ORR (95% CI)	72% (62, 81) [mITT[g]; N=101], 66% (56, 75) [ITT[h]; N=111]	55% (44, 65) [mITT[g]; N=99], 37% (29, 45) [ITT[h]; N=147]	73% (66, 79) [mITT[g]; N=216], 60% (54, 66) [ITT[i], N=298]	50% (40, 60), 52% (43, 60)	49% (39, 59), 51% (43, 59)
CRR (95% CI)	51% (not reported) [mITT[g]; N=101], 47% (not reported) [ITT[h]; N=111]	41% (not reported) [mITT[g]; N=99], 28% (not reported) [ITT[h]; N=147]	53% (46, 60) [mITT[g];N=216], 43% (37, 49) [ITT[i], N=298]	35% (26, 45), 40% (32, 48) Prior CAR-T: 32% [N=38], 37% [n=52]	34% (25, 44), 40% (32, 48) Prior CAR-T: 29% [N=35], 35% [n=49]
DOCR [months], median (95% CI)	NE (0.4, 17.3)	NE (10.0, NE)[j]	26.1 (23.1, NR)	NE (18.2, NE), NE (16.8, NE)	NE (18.4, NE), NE (16.8, NE)
DOR [months], median (95% CI)	14.0 (0, 17.3)	NR (10.0, NE)	16.8 (8.0, NR)	14.4 (8.6, NE), 16.8 (10.4, NE)	14.4 (8.6, NE), 16.8 (11.4, NE)

CCOD=clinical cutoff date; CI=confidence interval; CR=complete response; FU=follow up; ITT=intent to treat; mDOR=median duration of responose; mDOCR=median duration of complete response; mITT=modified intent to treat; mo.=month; NE=not estimable/evaluable; NR=not reached; PMBCL=primary mediastinal B-cell lymphoma. Note for responses, all are best overall response.
a Yescarta SmPC; bKymriah SmPC; c Breyanzi SmPC; d Achieved less than CR to last prior therapy; e Yescarta EPAR; f Breyanzi USPI; g modified ITT, limited to patients receiving the CAR-T construct; h intent to treat/all patients enrolled (patients underwent leukapheresis); i Among ITT patients who underwent leukapheresis and had radiographically evaluable disease; j Kymriah EPAR.

The COMP agreed with the sponsor that the patient population included in the expanded efficacy population from study NP30179 is older that those included in the pivotal studies for the CAR-T cell therapies, but whether this might have any impact on the efficacy results has not been established. In addition, the patients who received liso-cel in its pivotal study appear to be comparable in terms of refractoriness to those treated with glofitamab. Nevertheless, around one third of the patients treated with glofitamab had already received and progressed after prior CAR-T cell therapy. The response rates observed with glofitamab in this subset (ORR 49%; CRR 35%) are consistent with those observed in the main efficacy population and show that patients who had failed prior CAR-T cell therapy responded to subsequent treatment with glofitamab.

Significant benefit of glofitamab in patients with r/r DLBCL will be further discussed separately for each of the CAR-T cell therapies.

Improved safety:

The sponsor summarised the main safety findings with glofitamab compared with the CAR-T cell therapies. The sponsor claimed that glofitamab has a more favourable safety profile compared with the approved CAR-T cell therapies, with a lower frequency of severe (Grade ≥ 3) adverse events (AEs). In particular, when comparing overlapping toxicities, the frequency of Grade ≥ 3 CRS with glofitamab was lower or comparable to those reported for the CAR-T cell therapies, and the frequencies of Grade ≥ 3 neurological AEs and Grade ≥ 3 haematological toxicities (neutropenia, febrile neutropenia, and

thrombocytopenia) were also lower with glofitamab compared with the CAR-T cell therapies (Table 6 and Table 7) in the cross-study comparisons with the known limitations of such comparison.

Table 6. Overview of adverse events with glofitamab and CAR-T Cell Therapies

	YESCARTA	**KYMRIAH**	**BREYANZI**	**Glofitamab[a]**	
Study	**ZUMA-1[b]**	**JULIET[c]**	**TRANSCEND[d]**	**NP30179 (CCOD: 15 June 2022)**	
Safety evaluable population	**101 patients (DLBCL)**	**111 patients (DLBCL)**	**269 patients (majority DLBCL)**	**154 patients primary safety population (DLBCL+PMBCL)**	**469 patients overall safety population (NHL)**
Any TEAE	100%	100%	99%	99%	98%
Grade 3-5 TEAE	95%	85%[e] (Grade 3-4)	79%	64%	62%
Serious Adverse Event	51%	50%[e]	NR	49%	55%
Deaths due to Adverse Event	NR	NR	NR	6%	5%

CCOD=clinical cutoff date; DLBCL=diffuse large B-cell lymphoma; NHL=non-Hodgkin's lymphoma; NR=not reported; SAE=serious adverse event; TEAE=treatment-emergent adverse event.
a AE reporting period: For glofitamab (NP30179 study), 90 days after the last dose of study treatment. After a period of 90 days from the last dose of study drug, investigators should report any deaths, serious AEs, or other AEs of concern that are believed to be related to prior treatment with study drug. The duration of AE reporting in studies of other therapies are not clearly described in the manuscripts;
b Neelapu et al. 2017; c Schuster et al. 2019; d Abramson et al. 2020; e Patients with events starting ≤ 8 weeks after infusion.

Table 7. Safety (Selected AEs) of glofitamab compared with CAR T-Cell therapies indicated for r/r DLBCL after ≥ 2 prior lines of therapy

Therapy / N, Safety	**YESCARTA[a] (DLBCL+PMBCL) N=108**		**KYMRIAH[b] (DLBCL) N=115**		**BREYANZI[c] (DLBCL+PMBCL) N=268**		**Glofitamab (DLBCL+PMBCL) N=154**		**Comparison of glofitamab to CAR T-cell therapies**
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade≥3	Any Grade	Grade ≥3	
Cytokine Release Syndrome	93%[d]	11%[d]	57%[e]	23%[b, e]	46%	4%	64%	4%	Lower or comparable frequency of Grade ≥ 3 CRS with glofitamab vs CAR T-cell therapies

Neurological AEs*	87%	31%	60%	19%	35%	12%	36%	2%	Lower frequency of Grade ≥ 3 NAEs with glofitamab vs CAR T-cell therapies
Neutropenia	UNK	93%[a]	97%[e]	82%[e]	UNK	76%[f]	38%	27%	Lower frequency of Grade ≥ 3 neutropenia with glofitamab vs CAR T-cell therapies
Febrile Neutropenia	36%[d]	31%[a]	17%[2]	17%[b, e]	9%	UNK	3%	3%	Lower frequency of Grade ≥ 3 febrile neutropenia with glofitamab vs CAR T-cell therapies
Thrombo-cytopenia	UNK	40%[g]	UNK	39%[f]	UNK	39%[f]	25%	8%	Lower frequency of Grade ≥ 3 thrombocyto-penia with glofitamab vs CAR T-cell therapies.

DLBCL=diffuse large B-cell lymphoma; PMBCL=primary mediastinal B-cell lymphoma; UNK=unknown.
Note: Blue text indicates where numbers from SmPC differ from USPI.
*For NAEs, glofitamab presents incidence of AEs within Nervous system disorders SOC or Psychiatric disorders SOC . Yescarta, Kymriah, and Breyanzi present incidence of AEs within a specific group of terms (defined in each respective label).
a Yescarta USPI; bKymriah USPI. CRS graded by Penn grading system; cBreyanzi USPI. CRS graded by Lee et al. 2014.; dYescarta SmPC. CRS graded by Lee et al. 2014; e Kymriah SmPC; f Grade 3 or Grade 4 laboratory abnormalities; g Prolonged thrombocytopenia.

The COMP considered that the claim of improved safety based on the frequencies of overlapping toxicities does not reflect the whole picture, and that biases due to differences in patient characteristic cannot be excluded. Moreover, a comparable proportion of patients experienced serious AEs across the pivotal studies. Given the limited experience with glofitamab thus far from a small single-arm study with limited follow-up, the claim of better safety in comparison to the approved CAR-T cell therapies cannot be concluded on at present stage and no adequate quantification is possible for the descriptive cross-study comparisons presented.

Major contribution to patient care

The sponsor argued that patients who require rapid disease control of their aggressive lymphoma are unlikely to be suitable candidates for CAR-T cell therapy because of significant waiting times before start treatment. For patients with suitable disease kinetics, failure of CAR-T cell manufacturing and access to a specialized center are additional barriers they may face. According to the sponsor, glofitamab offers a significant benefit to patients with r/r DLBCL by being readily available when needed and providing rapid disease control and durable responses.

The COMP acknowledged the sponsors' argument that treatment with glofitamab requires no bridging- or pre-treatment therapy and can be used in all centres specialised in treating oncology patients without delays to patients suffering from a highly aggressive disease. However, it should be recalled that a product's claim of major contribution to patient care may not 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. 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" (available at: https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=OJ:JOC_2016_424_R_0003&from=EN).

Moreover, efficacy data for glofitamab from the subset of patients in the pivotal study who would be considered ineligible for the three approved CAR-T cell therapies, may be relevant for the COMP to evaluate such a claim.

Significant benefit of glofitamab versus Kymriah:

The sponsor claimed significant benefit of glofitamab versus Kymriah based on improved efficacy. When comparing the efficacy results for the ITT populations excluding patients with PMBCL (N=149 for glofitamab vs. N=167 enrolled/leukepheresed for Kymriah), glofitamab demonstrated improved efficacy over Kymriah based on higher response rates:

- The ORR and CRR for glofitamab (ORR 51%; CRR 40%) were both higher than those reported for Kymriah (ORR 37%; CRR 28%).
- With median follow-up for 13.4 months, median DOR for glofitamab was 16.8 months at the latest DCO and is likely to increase with longer follow-up. Median DOR for Kymriah was not reached at the latest DCO of its pivotal study (median follow-up 7.7 months; range: 0.4-50.0).
- Median DOCR was not reached for glofitamab at the latest DCO, at which time 76% of CRs in the pooled efficacy population were still ongoing. Median DOCR was also not reached for Kymriah at the latest DCO of its pivotal study (Table 5).

As already noted, patients receiving glofitamab in study NP30179 were older than those enrolled to receive Kymriah in the pivotal study JULIET (median age: 66.5 years vs. 58 years). Patients in the expanded efficacy population from study NP30179 were also more heavily pre-treated as all had received at least 2 prior lines of therapy (range: 2-7), whereas the JULIET study included patients with 1 or more prior lines (range: 1-6). Moreover, more patients treated with glofitamab were refractory to their prior therapies (Table 4). As such, patients in study NP30179 may represent a harder to treat population than the patient population of the pivotal study for Kymriah.

The sponsor also claimed significant benefit of glofitamab over Kymriah based on improved safety. Glofitamab had lower frequencies of Grade ≥ 3 (4% vs. 23%), Grade ≥ 3 neurological AEs (2% vs. 19%), and hematological toxicities including neutropenia (any grade: 38% vs. 97%; Grade ≥ 3: 27% vs. 82%), febrile neutropenia (3% vs. 17%), and thrombocytopenia (Grade ≥ 3: 8% vs. 39%; Table

7). The COMP considered that given the limited experience with glofitamab thus far, the claim of better safety in comparison to Kymriah cannot be concluded on at present stage and no adequate quantification is possible in the proposed indirect comparison.

Significant benefit of glofitamab versus Yescarta:

The sponsor claimed significant benefit of glofitamab versus Yescarta based on broadly on improved efficacy with comparable CRR and more durable responses in a harder to treat population. Patients receiving glofitamab in study NP30179 were older than those enrolled to receive Yescarta in the pivotal study ZUMA-1 (median age: 66.5 years vs. 58 years). Patients in the expanded efficacy population from study NP30179 were also more heavily pre-treated as all had received at least 2 prior lines of therapy (range: 2-7), whereas ZUMA-1 included patients with 1 or more prior lines (range: 1-10). Moreover, more patients treated with glofitamab were refractory to their prior therapies (Table 5).

According to the sponsor when comparing the efficacy results for the ITT populations (N=149 for glofitamab excluding patients with PMBCL vs. N=111 enrolled/leukapheresed for Yescarta including patients with PMBCL), glofitamab demonstrated broadly comparable CRRs and more durable responses per IRC assessment as compared to Yescarta:

- IRC-assessed ORR for glofitamab (51%) was lower than the ORR for Yescarta (66%), however, the CR rates are considered to be broadly comparable (40% vs. 47%, respectively) considering the larger proportion of patients with refractory disease in study NP30179.
- Median DOR for glofitamab of 16.8 months was longer than the median DOR of 14 months reported for Yescarta at the 12-month analysis of its pivotal study (median follow-up of 15.1 month).
- Median DOCR was not reached for glofitamab at the latest DCO (median follow-up 13.4 months), at which time 76% of CRs in the pooled efficacy population were still ongoing. Median DOCR was also not reached for Yescarta at the at the 12-month analysis of its pivotal study (Table 5).

In an updated analysis from the Yescarta ZUMA-1 trial with a median follow-up of 27 months (Locke et al. 2019), the median DOR per investigator assessment was reported to be 11.1 months (95% CI: 4.2, NE) and median INV-DOCR was still not reached (95% CI: 12.9, NE); 39/84 patients (46%) had ongoing responses at the data cut-off including 37/59 patients (63%) with ongoing complete responses. In the glofitamab study NP30179, a supporting cohort of 97 patients with DLBCL NOS, trFL and HGBCL treated with glofitamab ≥ 10 mg doses had been followed for a similar length of time (26 months) and showed highly durable responses (Table 4): at the 15 June 2022 CCOD, median DOR in this supporting cohort was 25 months (95% CI: 9.4, NE) for IRC-DOR and median DOCR had still not been reached (95% CI: 17.9, NE), with 63% of complete responders (per IRC) still in remission. These data support that glofitamab achieves equally durable complete responses as Yescarta in 3L+ r/r DLBCL in the view of the sponsor.

Furthermore, the sponsor discusses that from a safety perspective, when comparing overlapping toxicities, glofitamab has a more favourable safety profile than Yescarta, with lower frequencies of Grade ≥ 3 CRS (4% vs. 11%), Grade ≥ 3 neurological AEs (2% vs. 31%), and haematological toxicities including neutropenia (Grade ≥ 3: 27% vs. 93%), febrile neutropenia (3% vs. 31%), and thrombocytopenia (Grade ≥ 3: 8% vs. 40%; Table 7). The same arguments as were described earlier in the report for a major contribution to patient care as compared with Yescarta was also put forward.

Regarding the claim on improved efficacy the COMP considered that the significant benefit of glofitamab over Yescarta is not considered established, based on the data presented. The median DOR for glofitamab of 16.8 months was longer than the median DOR of 14.0 months reported for Yescarta

at the 12-month analysis of its pivotal study (median follow-up of 15.1 month). However, the median DOR was not reached for Yescarta at the additional 24-month analysis with a median follow-up of 27.1 months and the ORR for glofitamab was also lower than that reported for Yescarta (51% vs. 66%).

The COMP considered that the claim of better safety and the arguments for a major contribution to patient care compared to Yescarta are not considered established based on the data provided.

In conclusion, the COMP considered that the sponsor should provide a more detailed overview of the baseline characteristics of the patient populations included in the comparator study ZUMA-1 versus the pivotal study NP30179 for glofitamab. Finally, the sponsor should submit a matching-adjusted indirect comparison of the efficacy outcomes between patients treated with Yescarta in ZUMA-1 versus patients treated with glofitamab in NP30179.

Significant benefit versus Breyanzi:

The sponsor claimed significant benefit of glofitamab versus Breyanzi based on comparable efficacy and improved safety. Patients receiving glofitamab in study NP30179 were older than those enrolled to receive Breyanzi in the pivotal study TRANSCEND (median age: 66.5 years vs. 62 years). Patients in the expanded efficacy population from study NP30179 were also more heavily pre-treated as all had received at least 2 prior lines of therapy (range: 2-7), whereas the TRANSCEND study included patients with 1 or more prior lines (range: 1-12). Slightly more patients treated with glofitamab were refractory to prior therapies (Table 5).

According to the sponsor, when comparing the efficacy results for the ITT populations (N=149 for glofitamab excluding patients with PMBCL vs. N=298 enrolled/leukepheresed for Breyanzi including patients with PMBCL), glofitamab demonstrated comparable efficacy to Breyanzi based on similar CRRs and durability of responses:

- IRC-assessed ORR for glofitamab (51%) was lower than the ORR for Breyanzi (60%), however, the CR rates were similar (40% vs. 43%, respectively) considering the more refractory patient population in study NP30179.
- Median duration of response for glofitamab of 16.8 months was identical to that reported for Breyanzi at the at the latest DCO of its pivotal study (16.8 months).
- Median DOCR was not reached for glofitamab at the latest DCO (median follow-up 13.4 months), at which time 76% of CRs in the pooled efficacy population were still ongoing. Median DOCR was 26.1 months for Breyanzi at the latest DCO of its pivotal study (median follow-up 19.9 months [range: 0.2-45]; Table 5), and 63% of complete responders were in remission for at least 12 months.

In the supporting cohort of 97 patients with DLBCL NOS, trFL and HGBCL treated with glofitamab ≥ 10 mg doses and followed for 26 months (Table 4), median DOR was 25 months (95% CI: 9.4, NE) and median DOCR had not been reached (95% CI: 17.9, NE), with 63% of complete responders still in remission at the CCOD (15 June 2022).

From a safety perspective, when comparing overlapping toxicities, the sponsor claims that glofitamab has a more favorable safety profile than Breyanzi, with similar frequency of Grade ≥ 3 CRS (4%), but lower frequencies of Grade ≥ 3 neurological AEs (2% vs. 12%) and hematological toxicities including neutropenia (Grade ≥ 3: 27% vs. 76%), febrile neutropenia (3% vs. 9%), and thrombocytopenia (Grade ≥ 3: 8% vs. 39%; Table 7). The same arguments as were described earlier in the report for a MCPC as compared with Breyanzi was also put forward.

The COMP agreed with the sponsor that the efficacy of glofitamab appears comparable based on the descriptive cross-study comparisons. However, since there is no data on patients pretreated with Breyanzi the significant benefit cannot only be justified based on similar efficacy. The COMP considered that the claim of better safety and the arguments for a major contribution to patient care compared to Breyanzi are not considered established based on the data provided.

In conclusion, the COMP considered that the sponsor should provide a more detailed overview of the baseline characteristics of the patient populations included in the comparator studies TRANSCEND versus the pivotal study NP30179 for glofitamab. In addition, the sponsor should submit a matching-adjusted indirect comparisons of the efficacy outcomes between patients treated with Breyanzi in TRANSCEND versus patients treated with glofitamab in NP30179.

Significant benefit based on efficacy in patients pre-treated with CAR-T cell therapy

The sponsor claimed significant benefit of glofitamab over tisa-cel and axi-cel based on the efficacy observed in patients who had failed (relapsed after/refractory to) prior treatment with these two CD19-directed CAR-T cell products, which represents a patient population at risk for poor clinical outcome.

Around one third of the patients (33%; 49/149) in the expanded efficacy population from study NP30179 had previously received CAR-T cell therapy at the latest DCO. Among these, 28 patients received tisa-cel and 13 patients received axi-cel as prior therapy, whereas 8 patients received a CAR-T cell therapy that was not further specified. Of note, none of the patients were reported to have received liso-cel (Breyanzi) possible due to its later approval in the EU (MA: 04/04/2022) compared to Yescarta and Kymriah and the timing relative to enrolment in study NP30179. However, there may be patients who were treated with liso-cel as investigational medicinal product in clinical trials which were captured under 'other' CAR-T cell products.

The ORR for the patients who received prior CAR-T cell therapy in the pooled efficacy population was 49% (24/19; 95% CI: 34, 64), consistent with the ORR reported for the overall population (51%; 95% CI: 43, 59). The median DOR among the responders was 14.4 months (95% CI: 6.7, NE). Glofitamab achieved a clinically relevant CR rate of 35% (17/49; 95% CI: 22, 50) in patients who received prior CAR-T cell therapy in the pooled efficacy population, also consistent with the results in the overall population (40%; 95% CI: 32, 48). The median duration of follow-up for DOCR with glofitamab at the latest DCO for the subset of patients with prior CAR-T cell therapy was 7.2 months. Of the 17 patients who achieved an IRC-assessed CR with glofitamab, 13 patients (76.5%) remained in CR at the DCO. The median DOCR was 14.4 months (95% CI: 8.6, NE). According to the sponsor, the response rates reported for this subset support a significant benefit of glofitamab when compared with other therapies used after at least two prior lines of therapy in the post-CAR T-cell setting.

The sponsor further highlighted that when looking at glofitamab response rates by the specific prior CAR-T cell therapy received (Kymriah, Yescarta, or "other"; Table 4), the observed ORRs of 38-54% and CRRs of 25-46% were consistent with the results for the overall post-CAR T-cell subset in the pooled efficacy population. Patients previously treated with axi-cel achieved the highest response rates with glofitamab compared with those treated with prior tisa-cel or with other CAR-T cell therapies.

Table 8. Glofitamab response rates by prior CAR-T cell therapy in patients with r/r DLBCL after ≥2 prior lines treated with glofitamab 2.5/10/30 mg (DCO: 15-Jun-2022)

Response rates with glofitamab:	**Prior Kymriah**	**Prior Yescarta**	**Prior Other CAR T Cells**
Cohorts D2 [Sub 2], D3, D5 (N=149)	N=28	N=13	N=8
n, IRC-CR[a]	9	6	2
IRC-CR Rate [95% CI]	32% [16, 52]	46% [19, 75]	25% [3, 65]
n, IRC-OR (CR+PR)[a]	14	7	3
IRC-OR Rate [95% CI]	50% [31, 69]	54% [25, 81]	38% [9, 76]

a Lugano classification (Cheson et al. 2014)

Among patients who had received prior treatment with tisa-cel, median DOR was 8.6 months (95% CI: 2.3, NE) and median DOCR was 14.4 months (95% CI: 8.6, NE). Owing to a small sample sizes and limited follow-up in those patients who had received prior treatment with axi-cel and prior 'other' groups, an analysis of median DOR/DOCR was not possible.

The efficacy analysis in the subset of patients with prior CAR-T cell therapy in the pooled efficacy population of study NP30179 showed that glofitamab offered benefit for patients who have already been treated with Kymriah and Yescarta as those who had progressed following treatment with one of these two products achieved an ORR of 50-54% and a CR rate of 32-46%. The sponsor did not report the durability of the responses observed among the responders previously treated with Yescarta because of limited follow-up in a small sample size. Although the responses observed 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 and whose disease was refractory to especially Yescarta prior to enrolment in the study was rather limited and the data immature. In addition, there was no efficacy data reported for patients who were pre-treated with Breyanzi. The sponsor argued that 8 of the patients pre-treated with CAR-T cell therapies recorded as "other" prior CAR-T cells might include patients pre-treated with Breyanzi.

Based on the above, the COMP considered that the efficacy in the Kymriah pre-treated patients is considered clinically relevant. However, the sponsor should provide an updated sub-analysis of all efficacy parameters measured and available to date for patients previously receiving CAR-T cell therapy.

Significant benefit versus Zynlonta

The sponsor claimed that the patient population of study NP30179 was more refractory and included a greater proportion of patients who had received prior CAR-T cell therapy compared with the study population of LOTIS-2 which formed the basis of the MA for Zynlonta (Table 11) and is therefore considered a harder to treat population than the study population for Zynlonta. Note, the results reported for Zynlonta include patients with DLBCL and PMBCL; as such, results for the MA populations for study NP30179 are also presented in the Table 5.

The sponsor claimed significant benefit of glofitamab over loncastuximab tesirine (Zynlonta) based on improved efficacy in terms of a higher rate of CRs and more durable response, with a fixed treatment duration of 12 cycles (8.3 months) and without the need for prolonged treatment (up to 1 year in the pivotal study LOTIS-2) or treatment until progression per the approved treatment paradigm (Zynlonta SmPC). The ORR for glofitamab in the pooled efficacy population of study NP30179, excluding patients with PMBCL, was similar to the ORR reported for Zynlonta (51% vs. 48%). Glofitamab achieved a higher CR rate compared with Zynlonta (40% vs. 25%). The median DOR for glofitamab was longer than that reported for

Zynlonta (16.8 months vs. 13.4 months). The median DOCR was not reached for glofitamab and Zynlonta at the latest DCOs. However, glofitamab appears to achieve more durable CR. The majority of patients who achieved a CR with glofitamab (76%; 45/59) remained in CR at the latest DCO of its pivotal study (median follow-up 7.7 months), compared with 44% (16/36) in the LOTIS-2 study for Zynlonta after a median follow-up of 8 months (Kahl et al. 2021). Furthermore, in the subset of patients who had received prior CAR-T cell therapy, the CR rate achieved with glofitamab was higher than that reported with Zynlonta (35% vs. 21).

Table 9. Baseline Characteristics and Efficacy Results in Patients with 3L+ r/r DLBCL Treated with Zynlonta (LOTIS-2 Study) and with Glofitamab (Study NP30179)

	Zynlonta[a] (DLBCL, PMBCL)	**Glofitamab 2.5/10/30 mg[b] (DLBCL, PMBCL)**		**Glofitamab 2.5/10/30 mg[b] (DLBCL)**	
	LOTIS-2 N=145	**Cohort D3 N=108**	**Cohorts D2 [Sub. 2] + D3 + D5 N=155**	**Cohort D3 N=102**	**Cohorts D2 [Sub. 2] + D3 + D5 N=149**
Age, median (range), years	66 (23-94)	66 (21-90)	66 (21-90)	66.5 (21-90)	67 (21-90)
Age ≥ 65 years	55%	54%	54%	56%	56%
Prior therapies, median (range)	3 (2-7)	3 (2-7)	3 (2-7)	3 (2-7)	3 (2-7)
Prior anti-CD20 therapy, n (%)	not reported	108 (100%)	155 (100%)	102 (100%)	149 (100%)
Prior CAR-T therapy, n (%)	14 (10%)[c]	38 (35%)	52 (34%)	35 (34%)	49 (33%)
Refractory status:					
Last therapy	58%	83%	85%	82%	84%
First line (primary refractory)	20%	60%	58%	60%	58%
Prior CAR-T	not reported	32%	30%	31%	30%
Overall response rate (95% CI)	48% (40, 57)	50% (40, 60)	52% (43.5, 60)	49% (39, 59)	51% (43, 59)
Complete response rate (95% CI)	25% (18, 33)	35% (26, 45)	40% (32, 48)	34% (25, 44)	40% (32, 48)
mDOR (95% CI), months	13.4 (6.9, NE)	14.4 (8.6, NE)	16.8 (10.4, NE)	14.4 (8.6, NE)	16.8 (11.4, NE)
mDOCR (95% CI), months	not reached	NE (18.4, NE)	NE (16.8, NE)	NE (18.4, NE)	NE (16.8, NE)

CAR-T=chimeric antigen receptor T cell; CI=confidence interval; CR=complete response; mDOCR=median duration of complete response; mDOR=median duration of response: NE=not estimable.
a Zynlonta EPAR. Median duration of follow-up (CCOD 01 March 2021): 7.8 months; b Median duration of follow up at 15 June 2022 CCOD: 15.0 months (Cohort D3), 13.4 months (Cohorts D2 [Sub. 2], D3, and D5 pooled); c Zynlonta OMAR.

The sponsor also claimed better safety of glofitamab over Zynlonta in terms of better tolerability based on lower incidences of treatment discontinuations due to AEs (9% vs. 21%, respectively), AEs leading to dose modifications (18% vs. 47%), and severe AEs (64% vs. 74%) including fatal AEs (5.8% vs.

8.8%). In contrast, there was a higher incidence of AEs related to treatment (94% vs. 82%) and serious AEs (49% vs. 41%) with glofitamab compared with Zynlonta (Table 10).

The sponsor noted that glofitamab has a different safety profile to that of Zynlonta. Although myelosuppression and infections were frequently reported AEs common to both glofitamab and Zynlonta, phototoxicity and oedema and effusion are important identified risks for Zynlonta and CRS and tumor flare are important identified risks for glofitamab. While CRS is the most common adverse drug reaction (ADR) for glofitamab, it is manageable with <1% of patients discontinuing glofitamab due to AEs. In contrast, increased gamma-glutamyltransferase is the most common ADR with Zynlonta and led to treatment discontinuation in 9% of the patients (Zynlonta SmPC).

Table 10. Safety summary for patients with 3L+ r/r DLBCL treated with zynlonta (LOTIS-2 Study) and with glofitamab (Study NP30179)

	Zynlonta[a]	**Glofitamab 2.5/10/30 mg[b]**
Number of patients with at least one:	**LOTIS-2 N=215**	**Cohorts D2 [Sub. 2] + D3 + D5 N=154**
Treatment-emergent adverse event	98.6%	98.7%
Adverse event related to treatment[c]	81.9%	93.5%
Grade ≥ 3 adverse event	74.4%	63.6%
Serious adverse event	40.5%	48.7%
Adverse event leading to treatment discontinuation	20.5%	9.1%
Adverse event leading to dose modification	47.4%	18.2%
Adverse event leading to death	8.8%	5.8%

a Zynlonta EPAR, Table 31.
b Update CSR NP30179 (CCOD 15 June 2022).
c Related to either study drug, obinutuzumab or glofitamab, in study NP30179.

The COMP agreed that the descriptive data presented indicate a numerically higher CR rate and longer median DOR in patients with r/r DLBCL who were treated with glofitamab in study NP30179 as compared to that reported for Zynlonta in its pivotal study LOTIS-2. However, a methodologically sound indirect treatment comparison has not been provided.

Given the limited experience with glofitamab 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.

In conclusion, the COMP considered that the sponsor should provide a more detailed overview of the baseline characteristics of the patient populations included in the pivotal studies LOTIS-2 for Zynlonta versus NP30179 for glofitamab. In addition, the sponsor should submit a matching-adjusted indirect comparisons of the efficacy outcomes between patients treated with Zynlonta in LOTIS-2 versus patients treated with glofitamab in NP30179.

Based on the data provided by the sponsor, a positive conclusion on the product's (glofitamab) significant benefit vis a vis the satisfactory methods Yescarta, Breyanzi, and Zynlonta cannot be drawn.

Overall conclusion COMP:

The significant benefit of glofitamab vis a vis the authorised medicinal products Yescarta, Breyanzi, and Zynlonta for the target patient population is not considered established based on the data presented. A more comprehensive discussion on the claim of significant benefit for glofitamab over these products is therefore needed. The COMP adopted a List of Questions on significant benefit aiming at clarifying the differences in key baseline characteristics of the patient populations included in the comparator studies and requesting matching-adjusted indirect comparisons of the efficacy outcomes between patients treated with Yescarta, Breyanzi, and Zynlonta versus patients treated with glofitamab. In addition, the reported best response and duration of response as achieved with treatment with glofitamab for those patients in study NP30179 who were pre-treated with Yescarta was requested. Finally, a more detailed discussion on the argument that glofitamab will confer a benefit to patients who would be considered ineligible for CAR-T cell therapy was invited.

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

The sponsor further justified the claim for significant benefit of glofitamab over axi-cel (Yescarta) liso-cel (Breyanzi), and loncastuximab tesirine (Zynlonta) in the third- and later lines setting for the target DLBCL population based on more mature efficacy data from the pivotal study NP30179 as requested.

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

The sponsor provided updated efficacy results with glofitamab in patients with DLBCL and PMBCL from study NP30179 based on a more recent DCO of 16-Jan-2023 with approximately 7 months extended follow-up. A summary of all efficacy parameters analysed in study NP30179 for patients treated with glofitamab after prior CAR-T cell therapy based on the latest DCO is presented in Table 11. Based on these updated results, follow-up for IRC-assessed DOR and DOCR was 9.8 months among the responders to glofitamab who received prior Yescarta. Median DOR was 12.6 months (95% CI: 6.7, NE) and median DOCR was 6.7 months (95% CI: 5.3, NE).

The sponsor clarified that because of the timing of the enrolment into study NP30179 compared with the approval of Breyanzi, no patients treated with prior CAR-T cell therapy had liso-cel specified as their prior CAR-T cell product. However, according to the sponsor, there is no scientific rationale for why the clinical efficacy with glofitamab would be any different after prior treatment with Breyanzi compared with that observed in the post-Kymriah or post-Yescarta setting. The target (CD19) and signalling domains (CD3 zeta) for the three CAR-T cell products are similar, with differences in the co-stimulatory domains: Kymriah and Breyanzi with 4-1BB (CD137) and Yescarta with CD28.

Table 11. NP30179: Overview of efficacy with glofitamab by prior CAR T-Cell therapy in patients with r/r DLBCL and PMBCL ≥ 2 prior lines treated with glofitamab 2.5/10/30 mg (DCO: 16 Jan 2023)

	Glofitamab monotherapy (DLBCL, PMBCL)			
	All **N=155**	**Prior CAR T** **N=52**	**Prior Kymriah** **N=29**	**Prior Yescarta** **N=15**
n, IRC-CR	62	19	9	8
IRC-CR Rate [95% CI]	40% [32, 48]	37% [24, 51]	31% [15, 51]	53% [27, 79]
n, IRC-OR (CR+PR)	80	26	14	9
IRC-OR Rate [95% CI]	52% [43, 60]	50% [36, 64]	48% [29, 67]	60% [32, 84]
Median DOCR (months) [95% CI]	26.9 [18.4, NE]	22.0 [6.7, NE]	22.0 [14.4, NE]	6.7 [5.3, NE]
n (%), responders without event	42/62 (68%)	13/19 (68%)	6/9 (67%)	5/8 (63%)
Median DOR (months) [95% CI]	18.4 [12.6, NE]	14.4 [6.7, NE]	14.4 [2.4, NE]	12.6 [6.7, NE]
n (%), responders without event	44/80 (55%)	14/26 (54%)	6/14 (43%)	6/9 (67%)
Median IRC PFS (months) [95% CI]	4.9 [3.4, 7.8]	3.7 [3.3, 13.4]	3.7 [2.0, 7.6]	8.3 [1.5, NE]
Median OS (months) [95% CI]	12.0 [7.9, 17.8]	8.9 [6.8, 23.4]	7.6 [6.3, 15.7]	15.7 [7.5, NE]

Study NP30179 pooled efficacy population, Cohorts D2 [Sub. 2], D3, D5, including patients with PMBCL.
Median follow-up for response: 18.5 months for overall group; 16.1 months in post-Kymriah group; 9.8 months in post-Yescarta group.

The sponsor also submitted supportive efficacy results from early-phase studies evaluating glofitamab in combination with other agents (no expected activity as monotherapy according to sponsor) in patients with r/r DLBCL to further support the benefit of glofitamab in patients treated with glofitamab post-Kymriah, post-Yescarta, and post-Breyanzi. However, these data are obtained in a different clinical setting and therefore not considered relevant for evaluating the significant benefit for glofitamab as monotherapy for r/r DLBCL in the third- and later lines setting.

Comparison of the patient population characteristics and the outcomes in the comparator studies ZUMA-1, TRANSCEND and LOTIS-2 versus the pivotal study NP30179 for glofitamab

A more comprehensive summary of the baseline characteristics of the patient populations included in the pivotal comparator studies ZUMA-1 for axi-cel (Yescarta), TRANSCEND for liso-cel (Breyanzi), and LOTIS-2 for loncastuximab tesirine (Zynlonta), and in the pooled efficacy population of study NP30179 for glofitamab (N=155 including PMBCL patients) is presented in Table 12.

Comparative discussion of glofitamab versus axi-cel (Yescarta)

According to the sponsor, patients in NP30179 seem to represent a harder to treat population than the study population of ZUMA-1 for axi-cel. While a numerically higher proportion of patients with prior autologous stem cell transplant (ASCT) was included in ZUMA-1 as compared to NP30179 (25% vs. 19%), the other baseline characteristics reported such as ECOG PS, IPI score, and disease stage were comparable between the two study populations. It should be noted, though, that a slightly higher proportion of patients received three or more prior lines in ZUMA-1 (69% vs. 61%) and more patients also had advanced disease stage III-IV (85% vs. 75%) compared to those included in NP30179.

The updated efficacy analysis for glofitamab (DCO: 16-Jan-2023) confirmed broadly comparable CRRs (40% vs. 47%) and more durable responses as compared to axi-cel (N=111 enrolled including patients with PMBCL). The median DOR for glofitamab of 18.4 months at a median follow-up of 21.2 months was longer than the median DOR of 11.1 months reported for axi-cel in its pivotal study with a median follow-up of 27.1 months (Locke et al., 2019). Yet, it should be noted that the ORR for glofitamab was lower than that reported for axi-cel (52% vs. 66%). The median DOCR was 26.9 months for glofitamab with 68% of CRs in the pooled efficacy population still ongoing at the time of the latest DCO, whereas it was not reached for axi-cel. When comparing the efficacy results for the CAR-T naïve subset in study NP30179, the response rates observed with glofitamab were broadly comparable, although consistently lower, to those reported with axi-cel. However, patients who responded to glofitamab achieved more durable responses than those treated with axi-cel. The median DOR for glofitamab was 24.8 months in CAR-T naïve patients versus 11.1 months for axi-cel.

Table 12. Baseline characteristics of patients enrolled in glofitamab study NP30179 compared with Yescarta (ZUMA-1), Breyanzi (TRANSCEND), and Zynlonta (LOTIS-2) studies including a comparison of efficacy

Baseline characteristic	**Yescarta [a] (DLBCL, PMBCL) N=101 (infused), N=111 (enrolled)**	**Breyanzi [g] (DLBCL, PMBCL) N=298 (enrolled)[¥]**	**Zynlonta[l] (DLBCL, PMBCL) N=145**	**Glofitamab (DLBCL, PMBCL) [DCO: 16-Jan-2023]**		
				All N=155	**Prior CAR-T N=52**	**CAR-T naïve N=103**
Age [years], median (range)	58 (23-76)	62 (18-82)	66 (23-94)	66 (21-90)	60 (21-78)	71 (26-90)
Age ≥ 65 years,%	24%	39%	55%	54%	33%	65%
Age ≥ 75 years,%	4%	8%	14.5%	22%	6%	30%
Male, %	67%	66.1%	58.6%	64.9%	76.9%	59.2%
Histology						
DLBCL NOS, %	74%	48%	88%[m]	71%	69%	72%
HGBCL	0[b]	16%	8%	7%	12%	4%
trFL	16%	29%	17%[n]	18%	14%	21%
PMBCL	8%	5%	5%	4%	6%	3%
Others	2%	2%	0	0	0	0
Prior therapies, median (range)	3 (1-10)	3 (1-8)[h]	3 (2-7)	3 (2-7)	3 (2-7)	2 (2-7)
1 prior line	2%	3% [h]	0	0	0	0
2 prior lines	29%	45% [h]	43%	39%	14%	52%
≥3 prior lines	69%	51% [h]	57%	61%	87%	48%
Refractory status[†]:						
Last therapy	66%[f]	44%[j]	58%[p]	85%	92%	81%
Primary refractory	26%[f]	20%[j]	20%[p]	59%	67%	54%
Refractory to CAR-T, %	N/A	N/A	3% [o]	30%	89%	N/A
Prior therapies:						
Prior CAR-T, n (%)	N/A	N/A	10%[o]	33.5%	100%	N/A

Time since last therapy, (months), n (range)	Data not reported	Data not reported	Data not reported	2.7 (0.3-147.3)	3.2 (0.5-18.6)	2.5 (0.3-147.3)
Prior ASCT, %	25%	36%	17%	19%	12%	22%
Disease stage, %:						
I-II	15%	27%[i]	23%	23%	29%	19%
III-IV	85%	72% [i]	77%	75%	67%	79%
Missing/unknown	N/A	1% [i]	N/A	3%	4%	2%
ECOG PS						
0	42%	41%[h]	40%	45%	56%	39%
1	58%	57% [h]	54%	55%	42%	60%
2	0	1% [h]	6%	1%	0	1%
IPI score						
≤2	53%	59% [i]	57%	48%	54%	45%
≥3	48%	41% [i]	Data not reported	52%	46%	55%
Missing	0	1% [i]	Data not reported	0	0	0
Bulky disease (10 cm), n (%)	17%	11% [i]	6%[p,q]	12%	6%	16%
Tumor Burden (SPD, mm^2), median (range)	3723 (171-23297)	2250[j] (850-5790)	Data not reported	3415 (49-40152)	3025 (49-32624)	3711.5 (180-40152)
Extranodal disease, n (%)	69%	52.3% [i]	Data not reported	61%	69%	57%
ORR (95% CI)	72% (62, 81)[c] [mITT[d]; N=101] [c], 66% (56, 75) [c] [ITT[h]; N=111] [c]	73% (66, 79) [mITT[d]; N=216], 60% (54, 66) [ITT[i], N=298]	48% (40, 57)	52% (43, 60)	50% (36,64)	52.4% (42, 62)
CRR (95% CI)	51% (not reported)[c] [mITT[d]; N=101] [c], 47% (not reported)[c] [ITT[e]; N=111] [c]	53% (46, 60) [mITT[d];N=216], 43% (37, 49) [ITT[k], N=298]	25% (18, 33)	40% (32, 48)	37% (24,51)	42% (32,52)
DOCR [months], median (95% CI)	NE (12.9, NE)[f]	26.1 (23.1, NR)	not reached	26.9 (18.4, NE)	22.0 (6.7,NE)	26.9 (18.4, NE)
DOR [months], median (95% CI)	11.1 (4.2, NE) [f]	16.8 (8.0, NR)	13.4 (6.9, NE)	18.4 (12.6, NE)	14.4 (6.7,NE)	24.8 (11.4, NE)
Median follow up [months]	27.1 [f]	19.9	7.8	21.2	14.6	21.2

a Yescarta EPAR.
b 6 patients presented HGBCL disease as per Locke et al. 2019.

c Yescarta SmPC.
d Modified ITT, limited to patients receiving the CAR-T construct.
e Intent to treat/all patients enrolled (patients underwent leukapheresis).
f Locke et al. 2019.
g Breyanzi SmPC.
h Breyanzi EPAR.
i Maloney et al. 2021.
j Abramson et al. 2020.
k Among ITT patients who underwent leukapheresis and had radiographically evaluable disease.
l Zynlonta EPAR.
m DLBCL NOS includes transformed DLBCL (arising from low-grade lymphoma 20%) per Zynlonta SmPC.
n Transformed DLBCL patients are not counted as separate category in the "Primary Category" in Table 21 of the Zynlonta EPAR. Transformed DLBCL is described under Additional subtypes within Table 21 of the Zynlonta EPAR and for the Zynlonta SmPC.
o Zynlonta Orphan Maintenance Assessment Report.
p Caimi et al. 2021.
q Patients with bulky disease, defined as any tumor ≥10 cm in longest dimension (added in Protocol Amendment 2), were excluded as per study protocol exclusion criteria.
¥ the denominator (n) changes based on the source.
† The definition of refractory status differs across studies. The study specific definitions are the following:
- ZUMA-1: Definition of primary refractory in the refractory subgroup according to the ZUMA-1 protocol: experienced disease progression as best response to first line therapy or had stable disease after at least 4 cycles of first line therapy with duration of stable disease no longer than 6 months from the last dose of therapy. Definition of refractory to last therapy: best response as progressive disease to last previous therapy (Locke et al. 2019).
- TRANSCEND: refractory if the best response less than complete response (Abramson et al. 2020)
- LOTIS-2: Refractory disease defined as no response to therapy (Caimi et al. 2021).
- NP30179: Patients who had no response or relapse within 6 months of first anti-lymphoma therapy end date of their first line therapy.

Comparative discussion of glofitamab versus liso-cel (Breyanzi)

The sponsor repeated that the patients who received glofitamab in study NP30179 seem to represent a harder to treat population than the study population of TRANSCEND for liso-cel. While a numerically higher proportion of patients who had received prior ASCT was included in TRANSCEND as compared to study NP30179 (36% vs. 19%), the enrolled patients in NP30179 included a greater proportion of patients with IPI score ≥3 (52% vs. 41%), extra-nodal disease (61% vs. 52%), and higher tumour burden. The other baseline characteristics reported, including ECOG PS, disease stage, and bulky disease, were comparable between the two study populations.

The sponsor argued that the updated results for glofitamab from study NP30179 (DCO: 16-Jan-2023) demonstrated comparable efficacy to liso-cel (N=298 enrolled including patients with PMBCL) based on similar CRRs (40% vs. 43%) and durability of the responses. The median DOR for glofitamab of 18.4 months (median follow-up of 21.2 months) was slightly longer than that reported for liso-cel of 16.8 months at the latest DCO of its pivotal study (median follow-up 19.9 months; range: 0.2-45.2). It should be noted that the ORR for glofitamab was lower than that reported for liso-cel (52% vs. 60%). The median DOCR was reported to be 26.9 months for glofitamab and 26.1 months for liso-cel at the latest DCO of its pivotal study. When comparing the efficacy results for the CAR-T naïve subset in study NP30179, the response rates observed with glofitamab were broadly comparable, although the ORR was somewhat lower, to those reported with liso-cel. The median DOR for glofitamab was 24.8 months in CAR-T naïve patients versus 16.8 months for liso-cel.

Comparative discussion of glofitamab versus loncastuximab tesirine (Zynlonta)

The sponsor repeated that the pooled efficacy population of study NP30179 is considered a harder to treat population than the study population of LOTIS-2 for loncastuximab. According to the sponsor, the population treated with glofitamab was more heavily pre-treated and included a greater proportion of patients who had received prior CAR-T cell therapy (34% vs. 10%). Moreover, the patient population in study NP30179 included a higher proportion of patients with IPI score 3-5 and bulky disease (12%

vs. 6%), as patients with bulky disease were excluded from LOTIS-2. The other baseline characteristics reported were comparable between the two study populations.

The sponsor claimed that the updated results from study NP30179 (DCO: 16-Jan-2023) confirmed a significant benefit of glofitamab based on improved efficacy over loncastuximab. The ORR for patients treated with glofitamab was comparable to the ORR reported for loncastuximab (52% vs. 48%), but the median DOR was longer for glofitamab than for loncastuximab (18.4 vs. 13.4 months). Glofitamab achieved a higher CRR in treated patients compared with loncastuximab (40% vs. 25%). The median DOCR was reported to be 26.9 months for glofitamab and was not reached for loncastuximab at the latest DCO of its pivotal study. However, patients treated with glofitamab appeared to achieve more durable CRs as the majority of patients who achieved a CR with glofitamab (68%; 42/62) remained in complete remission at the DCO (median duration of CR follow-up: 18 months), compared with 44% (16/36) in LOTIS-2 after a median follow-up of 8 months (DCO: 01-Mar-2021; Kahl et al., 2021).

Relative efficacy of glofitamab versus Yescarta, Breyanzi, and Zynlonta using MAICs

The sponsor has conducted as requested indirect treatment comparisons (ITC) on efficacy endpoints (OR, CR, OS, PFS) and tolerability (based on a proxy of AE leading to dose continuation) between glofitamab and Yescarta, Breyanzi, and Zynlonta based on the matching-adjusted indirect comparison (MAIC) methodology. The MAIC analyses presented used data from 155 patients with r/r DLBCL ($\geq$ 2 lines of prior therapy) who received the registrational dose of glofitamab (2.5/10/30 mg) in Cohorts D2 [Sub. 2], D3, and D5 of study NP30179 at the DCO date of 15-Jun-2022, and published data for the comparator products identified through a systematic literature review (SLR) in r/r DLBCL (latest search date September 2022), and manual searches after September 2022. For all comparators, their respective pivotal studies (ZUMA-1, TRANSCEND NHL 001, and LOTIS-2 for Yescarta, Breyanzi, and Zynlonta, respectively) were used.

Confounders (prognostic factors and effect modifiers) to adjust for were classified as either high, medium, or low priority according to clinical feedback from a panel of external international key opinion leaders (KOLs) in lymphoma. The following were classified with high priority: IPI score (age, ECOG PS, Ann Arbor stage, high lactate dehydrogenase [LDH] levels, and presence of extra-nodal disease), refractoriness to either first line, last line or any line of treatment (some advisors ranked this as lower priority compared to the previous two), double/triple hit (DH/TH) lymphoma, histological subtype (e.g., HGBCL, PMBCL, or DLBCL/trFL), early relapse after SCT (<12 months), and number of prior treatment lines (e.g., 3 vs. >3 [no clinically established threshold], or median). Medium priority was assigned to bulky disease (no clinically established threshold), chemotherapy refractoriness, prior treatment with (or refractoriness to) rituximab and an anthracycline therapy, rituximab refractoriness, and early relapse from last line of treatment (<12 months), or, alternatively, time since completion of last therapy. Low priority was given to prior SCT, cell type of origin of the disease, bone marrow involvement, primary bone marrow transplant, and primary diagnosis (DLBCL versus non-DLBCL/ indolent lymphoma).

MAIC results versus loncastuximab tesirine (Zynlonta)

The latest available efficacy data (DCO: 01-Mar-2021) from the pivotal study LOTIS-2 (N=145; as-treated population) for loncastuximab (Zynlonta) was used, whereas data on baseline characteristics available from all LOTIS-2 related publications was considered to inform the list of confounders to adjust for in the comparison.

According to the sponsor, the base-case (BC) analysis maximizes the bias/variance trade-off while controlling for all available relevant confounding factors (as per clinical opinion). The differences in

baseline characteristics pre- and post-adjustment between the glofitamab and Zynlonta patient cohorts considered in the analysis are reported in Table 13.

Table 13. Baseline Characteristics with and without MAIC Weighting: Glofitamab All Patients Matched to Zynlonta As-Treated Population (LOTIS-2), All Available Matching Covariates

Variable	**Glofitamab unweighted (n=155)**	**Glofitamab weighted (ESS=72.3)** **Base case**	**Zynlonta (n=145)** **(Caimi et al., 2021, Zynlonta EPAR, Kahl et al., 2021)**
Age (mean)	63.05	62.70	62.70
ECOG PS ≥1 (%)	50	60	60
Ann Arbor Stage III–IV (%)	77	77	77
High LDH (%)	70	70	70
IPI 3–5 (%)	52	43	43
Double/triple hit lymphoma (%) *	12	10	10
PMBCL histology (%)	4	5	5
Refractory to 1st line † (%)	23	23	23
Refractory to last line † (%)	55	66	66
>2 prior therapies ‡ (%)	65	57	57
Bulky disease ≥10 cm (%)	14	6	6
Cell type GCB (%)	43	33	33
Cell type ABC/non-GCB (%)	33	16	16
Prior SCT (%)	19	17	17

* Differences in the proportion of patients with HGBCL across trials were not adjusted for, as the proportion of patients with double-hit/triple-hit lymphoma was considered to be inclusive of these patients. In fact, the proportion of patients with HGBCL in LOTIS-2 was only reported for patients with double-hit/triple-hit lymphoma (i.e., it did not include patients with HGBCL NOS) and it was lower than that of all patients with double-hit/triple-hit lymphoma irrespective of the histology.
† Refractory disease defined as no response to therapy.
‡ Previous HSCT is included; for patients who received an autologous transplant, the mobilisation regimen was considered a line of therapy if it was chemotherapy-based and distinct from the other previous lines of treatment.

The effective sample size (ESS) for glofitamab reduced to approximately 72 patients after adjustment, indicating that there are differences in baseline characteristics between the two study populations. It was noted that the current follow-up for patients on glofitamab appears comparable to that for patients on Zynlonta and that progression and responses were based on the Lugano criteria in both studies.

The sponsor summarised that despite being associated with limitations and requiring longer follow-up data to confirm the findings, evidence from the MAIC vis-à-vis Zynlonta was overall supportive of the following conclusions:

- The MAIC results showed a strong trend in favour of glofitamab compared to Zynlonta with respect to the likelihood of achieving a CR (per IRC), with none of the two OR CIs crossing one. Moreover, the MAIC results showed a numerical trend in favour of Zynlonta compared to glofitamab with respect to the durability of CRs (per IRC). The results of comparisons on IRC-assessed CR are presented in Table 14. A numerical trend in favour of glofitamab compared to Zynlonta with respect to the likelihood of achieving an ORR (per IRC) and with regards to the durability of the responses were also shown, although both OR CIs for ORR and both HR CIs for DOR crossed one. The sponsor expressed that this indicates that there is relatively strong evidence supporting

glofitamab being superior to Zynlonta with respect to achieving a CR, but not strong evidence with respect to ORR, DOCR and DOR as per IRC assessment.

Table 14. CR (IRC) Unadjusted and Match-Adjusted Indirect Comparisons: Glofitamab All Patients Matched to Zynlonta As-Treated Population (LOTIS-2), All Available Matching Covariates

Arm	**OR (95% CI, unadjusted robust SE)***	**OR (95% CI, perc. bootstrap)***	**OR (95% CI, BCA bootstrap)***	**Bootstrap p-value**
Glofitamab	2.019 (1.23, 3.312)			
Glofitamab weighted		2.417 (1.523, 3.637)	2.417 (1.572, 3.778)	<0.001
Zynlonta				

Ratios >1 favor glofitamab.

- Columvi can be seen as comparable versus Zynlonta, or even superior for some efficacy outcomes (CRR, Table 14) and tolerability to Zynlonta as a treatment option for r/r DLBCL patients in the third- and later lines setting. As a note, it is also worth pointing out that the proportion of patients who received prior treatment with CAR-T cell therapies in the glofitamab population after filtering and MAIC-weighting remained higher (~28.3%) than that in the Zynlonta population (approximately 9%).

MAIC results versus axi-cel (Yescarta) and liso-cel (Breyanzi)

The sponsor also presented MAIC results versus axi-cel (Yescarta) and liso-cel (Breyanzi), but this will not be discussed in detail in this report as the efficacy observed with glofitamab in patients who had progressed after prior treatment with the approved CD19-directed CAR-T cell products is considered sufficient to support a claim of significant benefit over both Yescarta and Breyanzi.

In summary, the MAIC results showed strong or mild numerical trends in favour of both axi-cel and liso-cel with respect to the likelihood of achieving either an ORR or a CR compared to glofitamab as well as numerical trends in favour of glofitamab with regards to the durability of the responses compared to axi-cel and liso-cel.

The sponsor argued that the MAIC results indicated that there is relatively strong evidence supporting that axi-cel is superior to glofitamab with respect to achieving an ORR and a CR (per investigator), but not strong evidence supporting superiority of liso-cel. On the other hand, there is not strong evidence supporting that glofitamab is superior to axi-cel and liso-cel with respect to DOR and DOCR, despite the trends noted from the results presented.

The sponsor emphasised that the results for the efficacy endpoints should be interpreted with caution, not only due to the relatively smaller ESS after adjustment and filtering for (complete) responders, but also because it is not possible to ensure that the prognostic factors and effect modifiers are balanced between the responder groups. In fact, the adjustments between each of the comparator studies and the pivotal study for glofitamab were performed using data on the combination of responder and non-responder groups for each treatment (to resemble the outcomes that would have been observed in randomized controlled trials [RCTs]), and a sufficiently informative set of baseline characteristics for responders only was not available from the comparator studies LOTIS-2, TRANSCEND, and ZUMA-1.

Efficacy of glofitamab in subsets of patient who would be ineligible for CAR-T cell therapy

The sponsor acknowledged that there currently are no published guidelines or clear consensus among physicians regarding exclusion criteria for CAR-T cell therapy. The decisions are made on clinical judgment and guidance provided in the approved SmPCs and each country/institution has its own definition of clinical ineligibility, mainly based on patients' age, performance status, and concomitant comorbidities. Many of the factors used to determine eligibility/ineligibility for CAR-T cell therapy are not concrete factors that can easily be extracted from the data collected as part of study NP30179 (e.g., disease kinetics, comorbidity index; Shouse et al., 2023; Mian et al., 2021) or are part of a combination of factors considered to determine the overall clinical picture for an individual patient. The sponsor also noted that patients with rapidly progressing disease are not necessarily ineligible for CAR-T cell therapy but equally may not be considered eligible since their disease kinetics would not allow them to wait for CAR-T cell manufacture and lymphodepletion.

The sponsor noted that it is challenging to retrospectively identify a population in study NP30179 that would be considered ineligible to receive CAR-T cell therapy because of the absence of clear guidelines and difficulties to identify/extract factors representing ineligibility for CAR-T cell therapy from the data collected. The sponsor has presented efficacy data for glofitamab in five groups of patients within the pooled efficacy population of NP30179 that could be considered as ineligible to CAR-T cell therapy (Table 15).

Table 15. NP30179: Overview of efficacy with glofitamab in subgroups considered to represent CAR T-Ineligibility (CCOD: 16 Jan 2023)

	Glofitamab monotherapy (DLBCL, PMBCL)			
		No Prior CAR T		
	All **N=155**	**All** **N=103**	**Age ≥ 75 years** **N=31**	**Refractory to last line, <8 weeks since last therapy** **N=37**
IRC-CR Rate, n (%)	62 (40.0%)	43 (41.7%)	15 (48.4%)	8 (21.6%)
IRC-OR Rate, n (%)	80 (51.6%)	54 (52.4%)	16 (51.6%)	14 (37.8%)
Median DOCR (months) [95% CI]	26.9 [18.4, NE]	26.9 [18.4, NE]	NE [15.6, NE]	NE [5.5, NE]
Median DOR (months) [95% CI]	18.4 [12.6, NE]	24.8 [11.4, NE]	NE [15.6, NE]	9.3 [2.2, NE]
Median IRC PFS (months) [95% CI]	4.9 [3.4, 7.8]	5.2 [3.3, 8.5]	7.8 [3.3, NE]	3.3 [1.5, 4.4]
Median OS (months) [95% CI]	12.0 [7.9, 17.8]	15.0 [7.8, 27.3]	16.9 [6.8, NE]	7.9 [4.7, 17.8]

In all these groups, glofitamab showed efficacy that is clinically meaningful in terms of response rates, DOR, PFS, and OS considering that these patients have exhausted all available therapies based on the sponsor's assumption for the analysis that they were not eligible for CAR-T cell therapy. Based on these analyses, the sponsor considered that glofitamab shows a significant benefit for patients who are ineligible to CAR-T cell therapy and have exhausted all available therapies.

COMP discussion

The COMP concluded that the updated efficacy analysis in the subset of patients with prior CAR-T cell therapy in the pooled efficacy population of study NP30179 confirmed that glofitamab offered benefit for those patients who have progressed or relapsed after prior treatment with axi-cel, in addition to tisa-cel, as they achieved high and sustained ORRs to glofitamab. The responses observed in these subgroups of patients can 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.

Regarding liso-cel, the COMP acknowledged that at the timing of the enrolment into study NP30179, Breyanzi was not yet authorised, therefore no patients treated with prior CAR-T cell therapy had liso-cel specified as their prior CAR-T cell treatment in study NP30179. The COMP also considered the durable responses to glofitamab observed in 52 patients who had been treated with prior CAR-T cell therapy as clinically meaningful and noted that they represented one third (33.5%; 52/155) of the pooled efficacy population of the study.

Based on the relatively large number of patients pre-treated with at least two of the approved CD19-directed CAR-T cell products for treatment of DLBCL, the high and sustained ORR observed in this patient population and the lack of a scientific rationale that efficacy post-liso-cel would differ from that observed post tisa-cel, as both CAR constructs include the same costimulatory endodomain derived from the 4-1BB molecule (CD137) in addition to target the same antigen, the COMP concluded that the benefit of glofitamab observed in the subset of patients in the pooled efficacy population of study NP30179 who have progressed or relapsed after prior treatment with tisa-cel could also be extrapolated to patients who have failed previous treatment with liso-cel. Therefore, the significant benefit of glofitamab over liso-cel in addition to tisa-cel and axi-cel, is considered justified based on a clinically meaningful benefit for patients with r/r DLBCL who have progressed or relapsed after prior treatment with the authorised CAR-T cell products in the third- and later lines setting.

The COMP considered that the comprehensive summaries presented of the baseline characteristics comparing the distribution of clinically important prognostic factors identified a priori (classified with high priority) for the r/r DLBCL and PMBCL populations from the pooled efficacy population of study NP30179 for glofitamab and the pivotal comparator studies ZUMA-1, TRANSCEND NHL 001, and LOTIS-2 for Yescarta, Breyanzi, and Zynlonta, respectively, revealed heterogeneity in the studied patient populations. Overall, from the summary presented, it seems that the baseline characteristics of the patient population in LOTIS-2 for Zynlonta is comparable to that included in study NP30179 for glofitamab with some differences (mainly higher proportion of patients being primary refractory and refractory to last line of treatment, as well as those who had received prior CAR-T cell therapies), while the study population in TRANSCEND for Breyanzi also is less heavily pre-treated and appears to have had a better prognosis at study entry than those included in study NP30179.

The naïve side-by-side comparison of results from the pivotal study LOTIS-2 for loncastuximab versus that for glofitamab provided sufficient evidence to support the claim of a clinically relevant advantage of glofitamab based on improved efficacy in terms of more durable anti-tumour responses and higher and sustained CRs compared to that obtained with loncastuximab in patients with r/r DLBCL in the third- and later lines setting. The MAIC results described below also showed a trend in favour of glofitamab compared to loncastuximab with respect to the likelihood of achieving a CR or an ORR and with regards to the durability of the responses. The COMP hence concluded that the improved and sustained CRs with glofitamab compared to loncastuximab can justify the significant benefit in r/r DLBCL.

The COMP noted that the observed imbalances in identified risk factors were adjusted for in the unanchored MAIC approach conducted for the patient populations in the pivotal studies. The sponsor also adjusted for covariates in the MAICs that were considered less important to clinical outcomes in DLBCL and were classified a prior as either medium or low priority, in addition to confounders that were identified as important and therefore classified as high priority. This approach led to substantial reductions in the ESS for the MAICs, with a down-weighting of 54% (83/155) and as much as around 80% of the pooled efficacy population in study NP30179 for the adjusted BC populations compared correspondingly to the populations from LOTIS-2 and each of the two pivotal studies for the CAR-T cell products axi-cel and liso-cel. The results for the MAIC versus Zynlonta are broadly in line with the findings from the descriptive side-by-side comparison within a potentially more difficult to treat patient population. The MAIC comparing glofitamab with the CAR-T cell products axi-cel and liso-cel are difficult to interpret and are therefore not considered sufficiently robust and reliable. Overall, the MAIC results did not provide conclusive evidence on improved efficacy especially versus axi-cel and liso-cel in view of the large reduction of the ESS and contradictory results across several efficacy parameters. The ESS for the MAIC versus loncastuximab was more acceptable.

The COMP acknowledged that the sponsor has adequately discussed and presented results from exploratory analyses in five different patient subgroups from study NP30179 that possibly could have been considered ineligible to receive CAR-T cell therapy. However, the efficacy results from the analyses presented cannot be taken into consideration as none of the factors identified to representing ineligibility for CAR-T cell therapy are contraindications for this class of products and, as also recognised by the sponsor, there are currently no guidelines or clear consensus among physicians regarding eligibility criteria for CAR-T cell therapy.

COMP conclusion

In conclusion the sponsor has provided clinical study data that demonstrated improved and sustained complete responses with Columvi 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 r/r DLBCL, after two or more lines of systemic therapy.

4. COMP position adopted on 17 May 2022

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 the patients covered by Columvi, the assumption that Columvi 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 complete responses with Columvi 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 Columvi, glofitamab for treatment of diffuse large B-cell lymphoma (EU/3/21/2497) is not removed from the Community Register of Orphan Medicinal Products.