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Committee for Orphan Medicinal Products

Orphan designation withdrawal 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	09 September 2021
EC decision	15 October 2021
EC registration number	EU/3/21/2497
Type II variation procedural history	
Rapporteur / Co-rapporteur	Thalia Marie Estrup Blicher / Jan Mueller-Berghaus
Applicant	Roche Registration GmbH
Application submission	29 July 2024
Procedure start	17 August 2024
Procedure number	EMA/H/C/005751/II/05
Invented name	Columvi
Approved therapeutic indication extension	Columvi in combination with gemcitabine and oxaliplatin is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma not otherwise specified (DLBCL NOS) who are ineligible for autologous stem cell transplant (ASCT) Further information can be found in the European public assessment report (EPAR) on the Agency's website: www.ema.europa.eu/en/medicines/human/EPAR/Columvi
CHMP opinion	27 February 2025
COMP review of orphan medicinal product designation procedural history	
COMP rapporteurs	Frauke Naumann-Winter / Maria Elisabeth Kalland
Sponsor's report submission	21 August 2024
COMP discussion and adoption of list of questions	18-19 February 2025
Oral explanation	18 March 2025
Sponsor's removal request	19 March 2025

2. Grounds for the COMP opinion

2.1. Orphan medicinal product designation

The COMP opinion that was the basis for the initial orphan medicinal product 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.

2.2. Review of orphan medicinal product designation at the time of marketing authorisation

The COMP opinion on the initial review of the orphan medicinal product designation in 2023 was based on the following grounds:

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.

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

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

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

Condition

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin's lymphoma (NHL) in adults. The disease comprises a group of fast-growing, aggressive lymphoid malignancies that accounts for around 30-40% of all NHL cases globally (Chaganti et al.,2016). This rare blood cancer is histologically characterised by dense proliferation of large, transformed mature B-cells with prominent nucleoli and basophilic cytoplasm, which typically express the pan B-cell antigens CD19, CD20, CD22, CD79a, as well as other surface markers characteristic for the B-cell lineage (Martelli et al., 2013). In addition to occurring de novo, DLBCL can arise through the transformation from different types of low-grade B-cell malignancy such as follicular lymphoma (FL), marginal zone lymphoma (MZL), or chronic lymphocytic leukaemia (Richter's transformation).

DLBCL is a heterogeneous B-cell neoplasm that includes tumours arising from germinal centre B-cells (GCB) and post-germinal centre B-cells. The 2016 World Health Organization (WHO) classification of lymphoid neoplasms recognizes germinal centre B-cell-like (GCB) and activated B-cell-like (ABC) as two subtypes of DLBCL with different prognosis with current therapies (Swerdlow et al., 2016). The molecular pathogenesis of DLBCL is complex and includes both genetic lesions that are relatively specific for this disease (i.e., rearrangements of B-cell lymphoma 6 [BCL6]) and molecular alterations

that are shared with other NHL variants. Most tumours have rearrangement of the immunoglobulin heavy and light chain genes and somatic mutations of the variable regions of these genes. MYC gene rearrangement is seen in 5-15% of DLBCL and is frequently associated with BCL2, and to a lesser extent with BCL6. Large cell lymphomas with MYC and BCL2 and/or BCL6 rearrangements are included in a separate category in the 2016 WHO classification. In the 5th edition of the WHO classification of haematolymphoid tumours with a focus on lymphoid neoplasms (WHO-HAEM5) from 2022, this has been re-categorised as DLBCL/ high-grade B-cell lymphoma (HGBL) associated with MYC and BCL2 rearrangements, while the MYC/BCL6 double hit lymphomas are now considered genetic subtypes of DLBCL, not otherwise specified (NOS) or of HGBL, NOS (Alaggio et al., 2022).

Patients with DLBCL often present with single or multiple rapidly enlarging symptomatic masses usually located in lymph nodes of the neck or abdomen, which is accompanied by systemic symptoms called "B symptoms" which include fever, weight loss and/or drenching night sweats (approximately 30% cases) and elevated serum lactate dehydrogenase (LDH) (>50% cases). The disease usually affects adults, most frequently around the age of 60 to 70 years, with a median age of 66 years at diagnosis, but it also rarely occurs in adolescents and children.

The approved extension of the therapeutic indication "Columvi in combination with gemcitabine and oxaliplatin is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma not otherwise specified (DLBCL NOS) who are ineligible for autologous stem cell transplant (ASCT)" falls within the scope of the designated orphan condition.

Intention to diagnose, prevent or treat

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

Chronically debilitating and/or life-threatening nature

DLBCL is a life-threatening disease with an aggressive natural history and is fatal if not treated. The clinical course can be debilitating due to constitutional symptoms such as fever, night sweats, and weight loss, local symptoms of lymphadenopathy such as pain and disfigurement, end-organ damage from disease involvement, and bone marrow failure that may lead to infections, anaemia, and thrombocytopenia (Armitage 1998; Cheson et al., 2014). The disease is life-threatening in patients not responding to treatment (Sehn and Salles 2021).

Once patients progress after 1st line treatment, salvage regimens can induce a second remission, but <50% of patients experience prolonged PFS with second line (2L) regimens and the 3-year PFS for patients that undergo ASCT is only 53% (Gisselbrecht et al., 2010). Even if patients are eligible for high-dose chemotherapy (HDCT) and ASCT, less than half will be cured (Seyfarth et al., 2006; Gisselbrecht et al., 2010).

No significant changes have occurred in the chronically debilitating and life-threatening nature of the condition since the orphan designation in 2021. The COMP has previously accepted that the clinical course of DLBCL can be chronically debilitating due to constitutional symptoms, local symptoms of lymphadenopathy, end-organ damage from disease involvement, and bone marrow failure that may lead to infections, anaemia, and thrombocytopenia, and life-threatening in patients not responding to treatment. The severe nature of DLBCL earlier acknowledged by the COMP remains acceptable for this procedure.

Number of people affected or at risk

At the time of the orphan designation in 2021 and the initial orphan maintenance in 2023, the COMP concluded that the condition was estimated to be affecting approximately 4.3 in 10,000 persons in the European Union (EU). The sponsor maintains the same figure for this maintenance procedure.

The sponsor has identified additional and updated sources as compared to the initial orphan maintenance application in 2023. These included updated DLBCL and NHL prevalence estimates for NORDCAN (2021), IKNL (2023), Slovenia Cancer Registry (2020), AIRTUM (2022), Robert Koch Institute (2019), in addition to REDECAN (2020) and Belgium Cancer Registry (2018) (Table 1).

The population-based registry data average for the 10-year limited-duration DLBCL prevalence estimate (relevant for the indication of glofitamab) is 4.35 per 10,000 (using data from the NORDCAN countries, IKNL in The Netherlands, Robert Koch Institute in Germany, and the Belgium Cancer Registry). The 5-year limited-duration DLBCL prevalence estimate is 2.55 per 10,000 (using data from NORDCAN, IKNL, Slovenia Cancer Registry, Robert Koch Institute, REDECAN, and the Belgium Cancer Registry). The 20-year limited-duration DLBCL prevalence estimate is 6.86 per 10,000 (using data from IKNL, and the Robert Koch Institute). Finally, the complete/lifetime DLCBL prevalence is 7.57 (using data from NORDCAN, Slovenia Cancer Registry, AIRTUM in Italy, Robert Koch Institute in Germany, and REDECAN in Spain).

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

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	2021	27,697,712	1.90	3.35	-	7.07
IKNL[b]	The Netherlands	2023	17,811,291	2.89	4.81	6.74	-
Slovenia Cancer Registry[c]	Slovenia	2020	2,123,103	1.64	-	-	5.40
AIRTUM[d]	Italy	2022	59,030,000	-	-	-	8.21
Robert Koch Institute[e]	Germany	2019	83,166,711	2.85	4.76	6.89	7.38
REDECAN[f]	Spain	2020	46,852,800	2.35	-	-	7.51
Belgium Cancer Registry[g]	Belgium	2018	11,431,406	2.34	3.93	-	-
HMRN (for reference)[h]	United Kingdom	2019		2.53	4.42	-	-
EU27 estimate[i]				**2.55**	**4.35**	**6.86**	**7.57**

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).

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 2021.
b Based on reported prevalence counts and population as of 2023 in The Netherlands.
c Based on extracting the total counted NHL prevalence cases for 2020 for the duration of interest (5 year=1179, lifetime=3835), multiplied by DLBCL to NHL incidence rate ratio for Slovenia in 2018 (29.6%), divided by the 2020 population in Slovenia.
d Based on the number of 2022 NHL prevalence count (n=156,400) and applying the country-specific DLBCL to NHL ratio of 31% divided by the 2022 population.
e Based on applying the German 2019 DLBCL to NHL ratio (37%) to the total NHL reported prevalence cases in 2019 for each period of capture. Complete/lifetime prevalence is reported as 25 years.
f Based on applying the Spanish DLBCL to NHL ratio (35.5%) to the total NHL-reported prevalence cases in 2020 at 5 years (n=31,052) and lifetime NHL prevalence per 10,000.
g Based on reported gender-specific 5- and 10-year DLBCL prevalence per 10,000 and applying gender-specific population of Belgium in 2019 as weights.
h Reported 5- and 10-year prevalence in HMRN per 10,000 reported in 2019.
i The EU27 estimate is based on the latest observed data. Each prevalence estimate for the EU27 is an average based on population-based registry data available.

The sponsor argued that the 10-year limited-duration prevalence is representative of the total number of cases relevant for the indication of glofitamab, as the non-cured cases were defined as: newly diagnosed, undergoing intensive treatment as either incident or relapsed cases (regardless of diagnosis cohort), have intensive monitoring, and have less intensive monitoring of up to 7-8 years (time period to reflect risk of relapse).

The proposed prevalence is consistent with the prevalence figures recently accepted by the COMP for DLBCL. In recent considerations, the COMP has agreed that a 10-year limited duration estimate best reflect the whole DLBCL population and should be used in the calculation since the cumulative relapse for DLBCL has been reported to peak at around 6-8 years and plateau thereafter (Maurer et al., 2014; Harrysson et al., 2021). As a sensitivity analysis, an incidence-based cohort model was presented that also resulted in a modelled prevalence of less than 5 in 10.000 people. The same conclusion as for the orphan designation can therefore be accepted for this procedure, that DLBCL affects approximately 4.3 in 10,000 people in the EU.

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

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

Existing methods

The treatment landscape for DLBCL has evolved significantly since the publication of the European Society for Medical Oncology (ESMO) clinical practice guidelines for DLBCL in 2015 (Tilly et al., 2015). First-line treatment remains chemoimmunotherapy with an anti-CD20 antibody and an anthracycline-based regimen, typically R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) or the more recently approved Polivy plus R-CHP, which achieves cure rates of 50-60%. For relapsed or refractory (r/r) DLBCL, second-line standard treatment for transplant-eligible patients includes platinum-based regimens in combination with rituximab such as R-ICE (ifosfamide, carboplatin, etoposide), R-DHAP (dexamethasone, high-dose cytarabine, cisplatin) or R-GDP (gemcitabine, dexamethasone, cisplatin) followed by HDCT and ASCT in chemo-sensitive cases (Gisselbrecht et al.,

2010; Crump et al., 2014). ASCT is generally reserved for younger, fit patients, but less than half are cured, with poor outcomes in those being refractory to frontline therapy or relapse within 12 months (Seyfarth et al., 2006; Gisselbrecht et al., 2010). For transplant-ineligible patients, regimens such as gemcitabine and oxaliplatin (GemOx) ± rituximab or gemcitabine, dexamethasone and cisplatin (GDP) ± rituximab are commonly used in first relapse (National Comprehensive Cancer Network, 2025). It should be noted that none of these regimens are specifically approved as second-line treatment for DLBCL.

The ESMO guidelines emphasise the lack of an established standard of care for patients with r/r DLBCL after two or more lines of systemic therapies. Since 2015, several new medicinal products have been approved in the EU in the r/r disease setting, including the CD79b-directed antibody-drug conjugate (ADC) polatuzumab (Polivy) in combination with bendamustine and rituximab (Pola-BR), the anti-CD19 monoclonal antibody tafasitamab (Minjuvi) in combination with lenalidomide (Tafa-Len), three CD19-directed chimeric antigen receptor (CAR)-T cell therapies, axicabtagene ciloleucel (axi-cel; Yescarta), tisagenlecleucel (tisa-cel; Kymriah) and lisocabtagene maraleucel (liso-cel; Breyanzi), the CD19-targeted ADC loncastuximab tesirine (Zynlonta), and the CD20 T-cell-engaging bispecific antibodies epcoritamab (Tepkinly) and odronextamab (Ordspono).

Columvi (glofitamab) received a conditional EU approval in 2023 (Product No. EMA/H/C/005751) as monotherapy for adults with r/r DLBCL after two or more lines of systemic therapy. The proposed extension of its indication in combination with gemcitabine and oxaliplatin (Glofit-GemOx) aims to include adult patients with r/r DLBCL NOS ineligible for ASCT in the second- and later-line settings (Table 2). The sponsor summarised the DLBCL treatment landscape in the European community. They also provided a table overview of medicinal product approved for r/r DLBCL in second- and later lines, highlighting those considered satisfactory methods relevant for evaluating the significant benefit of the proposed extension of indication (Table 3).

Table 2. DLBCL Treatment Landscape (EU)

<table>
<tr><th>Patient segment</th><th>1L</th><th colspan="2">2L</th><th>3L and beyond</th></tr>
<tr><td>All patients</td><td>R-CHOP or R-CHOP-like regimens
Polivy + R-CHP</td><td colspan="3"></td></tr>
<tr><td rowspan="4">Transplant-eligible</td><td rowspan="4"></td><td colspan="2">intensive salvage regimens (R-DHAP/ICE/GDP)</td><td rowspan="3"></td></tr>
<tr><td colspan="2">HDCT + ASCT</td></tr>
<tr><td colspan="2">Yescarta[a], Breyanzi[a]</td></tr>
<tr><td colspan="3">allogeneic transplant</td></tr>
<tr><td>Transplant-ineligible</td><td></td><td colspan="3">platinum- and/or gemcitabine-based regimens (R-GemOx)
Columvi + GemOx*
Polivy + BR
Minjuvi + lenalidomide</td></tr>
</table>

All patients		Columvi (monotherapy) Kymriah, Yescarta, Breyanzi Zynlonta Tepkinly Ordspono
	Clinical trials with novel drugs (including new MoA) and new combinations	

ASCT=autologous stem cell transplant; BR=bendamustine + rituximab; GemOx=gemcitabine + oxaliplatin; HDCT=high-dose chemotherapy; MoA=mechanism of action; R-CH(O)P=rituximab, cyclophosphamide, doxorubicin, (vincristine,) and prednisone; R-DHAP=rituximab, dexamethasone, cytarabine, and cisplatin; R-GDP=rituximab, gemcitabine, cisplatin, and dexamethasone; R-ICE=rituximab, ifosfamide, carboplatin, and etoposide.

* Current Type II variation.

a Relapse <12 months or primary-refractory disease. Although transplant eligibility is not explicitly stated in the indication statement, the registrational trials included patients that were eligible for transplant (per section 5.1 of the SmPCs).

Polivy (Pola-BR) and Minjuvi (Tafa-Len) are authorised for use in transplant-ineligible patients in the second- and later-line settings, aligning with the target patient population of the proposed indication extension. These therapies are hence considered satisfactory methods relevant for evaluating the significant benefit of Columvi (Glofit-GemOx) and will be further discussed below under the significant benefit section. In contrast, Yescarta and Breyanzi, while authorised for use in second- and later lines, their indications in second line are restricted to patients with primary-refractory disease and those with early relapse (within 12 months) after first line chemoimmunotherapy. These therapies are therefore not considered satisfactory methods for the entire patient population covered by the proposed indication extension for Glofit-GemOx. Furthermore, the therapies restricted to third- and later-line settings do not fully align with the proposed indication extension and are not considered satisfactory for the entire target patient population.

Table 3. Medicinal products authorized in the EU for the treatment of adults with 2L+ r/r DLBCL

Product (INN)	**Therapeutic indication per SmPC**	**Satisfactory method**
Polivy (polatuzumab vedotin)	Polivy in combination with bendamustine and rituximab is indicated for the treatment of adult patients with r/r DLBCL who are not candidates for haematopoietic stem cell transplant.	**Yes**, as there is a complete overlap with the proposed extension of the therapeutic indication of glofitamab
Minjuvi (tafasitamab)	Minjuvi 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.	**Yes**, as there is a complete overlap with the proposed extension of the therapeutic indication of glofitamab

Product (INN)	Therapeutic indication per SmPC	Satisfactory method
Yescarta (axicabtagene ciloleucel)	Yescarta is indicated for the treatment of adult patients with DLBCL and high-grade B-cell lymphoma (HGBL) that relapses within 12 months from completion of, or is refractory to, first-line chemoimmunotherapy. Yescarta is indicated for the treatment of adult patients with r/r DLBCL and primary mediastinal large B-cell lymphoma (PMBCL), after two or more lines of systemic therapy.	Not satisfactory due to partial overlap given that the indication for Yescarta in the second line is restricted to patients with primary-refractory disease or those who relapse within 12 months of first-line therapy
Breyanzi (lisocabtagene maraleucel)	Breyanzi is indicated for the treatment of adult patients with DLBCL, high grade B-cell lymphoma (HGBCL), primary mediastinal large B-cell lymphoma (PMBCL) and follicular lymphoma grade 3B (FL3B), who relapsed within 12 months from completion of, or are refractory to, first-line chemoimmunotherapy. Breyanzi is indicated for the treatment of adult patients with r/r DLBCL, primary mediastinal large B-cell lymphoma (PMBCL) and follicular lymphoma grade 3B (FL3B), after two or more lines of systemic therapy.	Not satisfactory due to partial overlap given that the indication in the second line for Breyanzi is restricted to patients with primary-refractory disease or those who relapse within 12 months of first-line therapy
Kymriah (tisagenlecleucel)	Kymriah is indicated for the treatment of adult patients with r/r DLBCL after two or more lines of systemic therapy	Not satisfactory since Kymriah only covers r/r DLBCL patients in the third- and later-line settings
Zynlonta (loncastuximab tesirine)	Zynlonta as monotherapy is indicated for the treatment of adult patients with r/r DLBCL and HGBL, after two or more lines of systemic therapy	Not satisfactory since Zynlonta only covers r/r DLBCL patients in the third- and later-line settings
Tepkinly (epcoritamab)	Tepkinly as monotherapy is indicated for the treatment of adult patients with r/r DLBCL after two or more lines of systemic therapy	Not satisfactory since Tepkinly only covers r/r DLBCL patients in the third- and later-line settings
Ordspono (odronextamab)	Ordspono as monotherapy is indicated for the treatment of adult patients with r/r DLBCL after two or more lines of systemic therapy.	Not satisfactory since Ordspono only covers r/r DLBCL patients in the third- and later-line settings

Significant benefit

The sponsor did not seek any protocol assistance from EMA to get advice on the approach for collecting the evidence needed to justify significant benefit of glofitamab over existing methods targeting the same patient population which is covered by the applied extension of indication for Columvi.

The claim of significant benefit is based on the results from the open-label, multicentre, Phase III randomized controlled study GO41944 (also known as STARGLO) of glofitamab with gemcitabine plus oxaliplatin (Glofit-GemOx) versus rituximab with gemcitabine plus oxaliplatin (R-GemOx) in patients with r/r DLBCL NOS after one line of systemic therapy who are ineligible for transplant, or after two or more lines of therapy. Patients were randomized 2:1 to receive Glofit-GemOx (N=183) or R-GemOx (N=91) for 8 cycles Q3W, followed by 4 additional cycles of glofitamab monotherapy for patients in the Glofit-GemOx arm. Randomization was stratified by number of previous lines of systemic therapy for DLBCL (1 vs. ≥ 2) and outcome of last systemic therapy (relapsed vs. refractory).

The efficacy data are based on 183 patients randomized to the Glofit-GemOx arm, and safety data are based on 172 patients who received at least one dose of glofitamab. The primary efficacy endpoint was overall survival (OS), with key secondary endpoints (hierarchically tested) of progression free survival (PFS), complete response (CR) rate, and duration of CR (DOCR), all based on an independent review committee (IRC) assessment using the Lugano Classification criteria (Cheson et al., 2014).

According to the sponsor, at the time of the prespecified primary analysis (cut-off date 29 March 2023), the study met its primary endpoint and demonstrated statistically significant and clinically meaningful improvement in OS for Glofit-GemOx over R-GemOx (stratified HR 0.59; 95% CI: 0.40, 0.89; log-rank p-value=0.010706) in the intent-to-treat (ITT) population. The study also demonstrated statistically significant and clinically meaningful improvements for Glofit-GemOx over R-GemOx in key secondary endpoints of IRC-assessed PFS (stratified HR 0.37; 95% CI: 0.25, 0.55; log-rank p-value<0.000001) and IRC-assessed CR rate (difference of 28.3%; 95% CI: 16.3, 40.3, CMH test p-value=0.0001). Although median DOCR (IRC) was longer for Glofit-GemOx (14.4 months; 95% CI: 14.4, NE) than with R-GemOx (NE; 95% CI: 6.4, NE), the HR (0.59; 95% CI: 0.19, 1.83) did not meet the threshold for statistical significance (unstratified log-rank p-value=0.3560).

The robust benefit in OS, PFS, and CR rate in the ITT population continued to be observed in the updated analysis (cut-off data 16 February 2024), with median follow-up of 20.7 months (range: 0-36). The stratified HR for OS (0.62; 95% CI: 0.43, 0.88) was highly consistent with the primary analysis results in the ITT population. The median OS in the Glofit-GemOx (25.5 months; 95% CI: 18.3, NE) was substantially longer compared with the R-GemOx arm (12.9 months; 95% CI: 7.9, 18.5). There was also a substantial difference in median IRC-assessed PFS in the Glofit-GemOx arm compared to the R-GemOx arm (13.8 vs. 3.6 months; HR 0.40; 95% CI: 0.28, 0.57), while the difference in IRC-assessed CR rate increased further in favour of Glofit-GemOx (difference of 33.2%; 95% CI: 21.0, 45.5). At the updated analysis, median DOCR (IRC) was not evaluable in the Glofit-GemOx arm (95% CI: 11.8, NE) and was 24.2 months (95% CI: 6.9, NE) in the R-GemOx arm (HR 0.59; 95% CI: 0.25, 1.35).

Significant benefit of glofitamab over polatuzumab vedotin (Polivy)

The sponsor claimed significant benefit of glofitamab over polatuzumab vedotin (Polivy) based on a clinically relevant advantage in terms of improved efficacy in the target patient population.

Polivy was approved in combination with BR (Pola-BR) for the treatment of adult patients with r/r DLBCL who are ineligible for HSCT, based on the results from a Phase Ib/II study GO29365. This study included a randomized Phase II part with DLBCL patients (N=80), which showed higher response rates and improved OS for Pola-BR compared to BR, a commonly used regimen in this setting (Polivy SmPC; Sehn et al., 2020). Patients in the study received polatuzumab vedotin (1.8 mg/kg) with rituximab

(375 mg/m^2) and bendamustine (90 mg/m^2) for 6 cycles Q3W. The primary efficacy endpoint of the randomized Phase II part was IRC-assessed CR rate at the end of treatment, measured by PET-CT using modified Lugano Classification criteria (Cheson et al., 2014). The study was initiated in 2014. The data cut-off (DCO) date for the marketing authorisation (MA) was 30 April 2018, with a median follow-up duration of 22.3 months for the Pola-BR arm in the randomized Phase II part (Polivy EPAR).

The baseline characteristics of the study population which formed the basis for the approval of Polivy in second- and later lines r/r DLBCL, namely 40 patients treated with Pola-BR in the randomized r/r DLBCL cohort of study GO29365 are summarized in Table 3, alongside the corresponding baseline characteristics of 183 patients randomized to the Glofit-GemOx arm in the STARGLO study (updated analysis). It is important to note the substantial difference in sample size between the Pola-BR and Glofit-GemOx populations.

The two populations were broadly similar in terms of demographic characteristics. However, the sponsor highlighted several differences, suggesting that patients receiving Pola-BR were more heavily pretreated and included a higher proportion of high-risk features compared to those receiving Glofit-GemOx. Specifically, the majority of patients treated with Glofit-GemOx (62.8%) had received only one prior line of therapy, whereas most patients treated with Pola-BR (72.5%) had received two or more prior lines. A smaller proportion of patients in the Glofit-GemOx population had undergone prior ASCT compared to the Pola-BR population (5.5% vs. 25.0%, respectively). Additionally, only patients in the Glofit-GemOx arm had received prior CAR T-cell therapy (7.1% vs. 0%), likely due to the limited availability of CAR T-cell therapy at the time study GO29365 was conducted (2014-2016). Notably, the first CAR T-cell therapies were approved in 2017 (in the US).

Compared to the Pola-BR population, the Glofit-GemOx population had a moderately lower proportion of patients with advanced Ann Arbor stage III/IV disease (85.0% vs. 67.2%) and refractoriness to the last therapy (75.0% vs. 61.2%). Differences were also observed in terms of International Prognostic Index (IPI) score 3-5 and cell of origin (COO). However, it is important to note that IPI score and COO in the r/r setting have less prognostic value than in the first-line setting, and a direct comparison of COO across the two studies may be misleading due to differences in the methods used for assessment.

Table 4. Key Baseline Characteristics for Patients Treated with Pola-BR (Randomized Cohort, GO29365) or with Glofit-GemOx (ITT, STARGLO)

	Pola-BRa **N=40**	**Glofit-GemOxb** **N=183**
Age, median (range), years	67.0 (33-86)	68.0 (22-88)
Age ³ 65 years	57.5%	63.4%
Sex, male	70.0%	57.4%
ECOG performance status (PS)		
PS 0	30.0%c	40.0%
PS 1	52.5%c	49.4%
PS 2	15.0%	10.6%
Histology, DLBCL NOS	95.0%	100%
Ann Arbor stage III/IV	85.0%	67.2%
Bulky disease (³ 7.5 cm)	25.0%	29.0%c
IPI score 3-5	55.0%	47.5%
Cell of origin:		
GCB	37.5%	32.8%
ABC/non-GCB	47.5%	56.3%

	Pola-BRa N=40	Glofit-GemOxb N=183
Prior therapies, median (range)	2 (1-7)	1 (1-4)
1 prior line	27.5%	62.8%
³ 2 prior lines	72.5%	37.2%
Prior ASCT	25.0%d	5.5%
Prior CAR T-cell therapy	0	7.1%
Refractory status:		
Last therapy	75.0%e	61.2%
Primary-refractoryf	52.5%	57.9%
Refractory to CAR-T	N/A	7.1%

a Polivy EPAR (initial MAA; GO29365 CCOD 30 April 2018).

b Update CSR GO41944 (STARGLO; CCOD 16 February 2024). Note, 7/183 patients (3.8%) in the Glofit-GemOx arm received Pola-BR in a prior line.

c Source: t_mh_char_bulk75_IT_16FEB2024_41944.

d Interim CSR GO29365 (CCOD 30 April 2018).

e Defined as no response or progression or relapse within 6 months of last anti-lymphoma therapy end date.

f Defined as no response or progression or relapse within 6 months of first anti-lymphoma therapy end date.

The sponsor also presented a naïve indirect side-by-side comparison of efficacy results for patients treated with Pola-BR in the randomized r/r DLBCL cohort of study GO29365 and those randomized to the Glofit-GemOx arm in the STARGLO study (updated analysis). Median follow-up was similar between the two cohorts (22.3 vs. 22.5 months). When comparing efficacy results, it is important to consider differences in study design: STARGLO is a Phase III randomized controlled trial, while the randomized Phase II part of study GO29365 evaluating Pola-BR versus BR was a smaller study.

According to the indirect comparison provided, Glofit-GemOx showed improved efficacy over Pola-BR in patients with r/r DLBCL with longer median OS (25.5 vs. 12.4 months) and median PFS (13.8 vs. 9.5 months), as well as slightly higher objective response rate (ORR; best overall response [BOR]: 68.3% vs. 62.5%) and CR rate (BOR: 58.5% vs. 50.0%). Median duration or response (DOR) for Pola-BR was 12.6 months, with a 12-month event-free rate of 50.2%. Median IRC-assessed DOCR and DOR were not reached for Glofit-GemOx at the updated analysis, but the results suggest more durable responses with Glofit-GemOx compared to Pola-BR. In STARGLO, with median follow-up for IRC-assessed DOCR of 13.6 months in the updated analysis, 73.8% (79/107) with IRC-assessed CR in the Glofit-GemOx arm remained in complete remission at the DCO (16 February 2024). Similarly, with a median duration of follow-up for IRC-assessed DOR of 14.3 months at the DCO date for the updated analysis, 66.4% (83/125) with IRC-assessed ORR in the Glofit-GemOx arm remained in remission (vs. a 12-month event-free rate of 66.9% for DOR).

Table 5. Key efficacy results for patients treated with Pola-BR (Randomized Cohort, GO29365) or with Glofit-GemOx (ITT, STARGLO)

	Pola-BR[a] **N=40**	**Glofit-GemOx[b]** **N=183**
ORR, % (95% CI)	BOR: 62.5% (45.8, 72.3) EOT: 45.0% (29.3, 61.5)	BOR: 68.3% (61.0, 75.0) --
CR rate, % (95% CI)	BOR: 50.0% (33.8, 66.2)[c] EOT: 40.0% (24.9, 56.7)	BOR: 58.5% (51.0, 65.7) --
Median DOCR (95% CI)	not reported	NE (11.8, NE)
Median DOR (95% CI)	12.6 (7.2, NE)	NE (17.6, NE)
12-month event-free rate	50.2%	66.9%
Median PFS (95% CI)	9.5 (6.2, 13.9)	13.8 (8.7, 20.5)
Median OS (95% CI)	12.4 (9.0, NE)	25.5 (18.3, NE)
Median OS follow-up (95% CI)	22.3 (20.5, 23.1)	22.5 (20, 24.5)

NE=not evaluable.
Response and PFS based on independent review committee for both studies.
a Polivy EPAR (initial MA; GO29365 CCOD 30 April 2018, median follow-up 22.3 months).
b Update CSR GO41944 (STARGLO; CCOD 16 February 2024, median follow-up 22.5 months).
c Interim CSR GO29365 (CCOD 30 April 2018, median follow-up 22.3 months).

The sponsor also presented several real-world studies of Polivy in combination with BR, which showed ORRs similar to those observed in the GO29365 study. However, CR rates were lower, and PFS and OS durations were shorter (Northend et al., 2022 [UK]; Argnani et al., 2022 [Italy]; Crombie et al., 2024 [US]) (Table 6).

Table 6. Real-world evidence of efficacy of Polivy (Pola-BR)

	Study GO29365 **N=40**	**Northend 2022** **N=78**	**Argnani 2022** **N=55**	**Crombie 2024** **N=69**
ORR	62.5%	65.8%	49.1%	59.4%
CRR	50.0%	39.7%	27.3%	18.8%
Median PFS	9.5 months	5.4 months	4.5 months	3.1 months
Median OS	12.4 months	10.2 months	9.0 months	7.8 months

Finally, in terms of improved efficacy, the sponsor argued that published data show lower efficacy of Polivy+BR compared to Glofit-GemOx in patients treated after prior CAR T-cell therapy. In STARGLO, 7.1% (13/183) treated with Glofit-GemOx had received prior CAR T-cell therapy: 7 patients had received Yescarta, 4 patients Kymriah, and 2 patients unspecified CAR T-cell products. All 13 patients were refractory to prior CAR T-cell therapy. This subset was heavily pretreated (median 3 prior lines) and more refractory than patients without prior CAR T-cell therapy. In the updated analysis (16 February 2024), ORR was 69% (9/13) and CR rate was 54% (7/13) for patients treated with Glofit-GemOx after prior CAR T-cell therapy. Median DOR and DOCR in this subset were 6.1 and 5.8 months, respectively, while median PFS and OS were 8.4 and 13.7 months (Table 7).

As previously noted, no patients in the Pola-BR study GO29365 had received prior CAR T-cell therapy. However, real-world data suggest lower efficacy of Polivy+BR compared to Glofit-GemOx after prior CAR T-cell therapy (Table 7).

Table 7. Treatment outcomes with Polivy and Columvi after prior CAR-T

	Pola-BR			**Glofit-GemOx[b]**
	Flores Avile 2022	**Gouni 2022**	**Iacoboni 2024[a]**	**STARGLO**
	N=6	**N=57[a]**	**N=67**	**N=13**
ORR	33%	44%	67%	69.2%
CR rate	0%	14%	38%	53.8%
Median PFS	not reported	10 weeks	7.5 months	8.4 months
Median OS	6.4 months	not reported	12.1 months	13.7 months

First therapy given after CAR T cells, unless otherwise stated.
a 34 patients (60%) received Pola-BR therapy immediately after CAR T-cell therapy, however, results for these patients are not presented separately; 23 patients received other treatments in-between (Gouni et al. 2022).
b Annex 2 (STARGLO; CCOD 16 February 2024).

Regarding safety, the sponsor emphasised that both Columvi (Glofit-GemOx) and Polivy (Pola-BR) have manageable and acceptable safety profiles in patients with r/r DLBCL who are ineligible for transplant.

COMP discussion

The COMP acknowledged that the patient populations in the pivotal studies for Pola-BR and Glofit-GemOx differ significantly in their baseline characteristics. Overall, patients receiving Pola-BR were more heavily pretreated compared to those receiving Glofit-GemOx. Notably, 72.5% of Pola-BR patients had received at least two prior lines of therapy, whereas 62.8% of Glofit-GemOx patients had received only one prior line. In addition, the Pola-BR cohort appeared to represent a population with more severe disease and poorer prognosis, as reflected by factors such as ECOG PS, Ann Arbor stage, and refractory status. Furthermore, CAR-T cell therapy was not available when the pivotal GO29365 study for Pola-BR was conducted, and no patients with prior CAR-T exposure were included in the study. Given these differences in baseline characteristics and disease severity, the naïve indirect side-by-side comparison of efficacy results is inherently limited. The slightly more favourable outcomes observed for Glofit-GemOx could potentially be attributed to these baseline imbalances rather than a true difference in treatment efficacy.

For Glofit-GemOx patients, an unusual observation was noted, where the median OS follow-up (22.5 months) was shorter than the median OS (25.5 months). This is contrary to expectations, as median follow-up is typically longer than median OS. The sponsor is therefore invited to provide clarification on this discrepancy and discuss the validity of the reported results in addition to the list of questions (see section 4).

Regarding the real-world data presented for Polivy, the lack of sufficient background information, including uncertainty quantification (e.g., confidence intervals), limits the interpretability of the findings. Consequently, no definitive conclusions can be drawn based on the data presented. In addition, comparisons of efficacy outcomes across subgroups within clinical studies or between studies are generally considered unreliable. The real-world evidence presented is therefore insufficient to

substantiate a claim of significant benefit for glofitamab over polatuzumab vedotin in patients with r/r DLCBL in the post-CAR-T setting.

Considering the baseline imbalances noted above, the COMP concluded that conducting a matching-adjusted indirect comparison (MAIC) would likely result in a substantially reduced effective sample size (ESS) for the adjusted STARGLO population. Nevertheless, assessing the overlap between the two study populations and evaluating the impact of an adjusted comparison on the treatment effect of glofitamab versus polatuzumab vedotin may still be worthwhile.

- ***Significant benefit of glofitamab over tafasitamab (Minjuvi)***

The sponsor claimed significant benefit of glofitamab over tafasitamab (Minjuvi) based on a clinically relevant advantage in terms of improved efficacy in the target patient population.

Minjuvi in combination with lenalidomide (Tafa-Len), followed by Minjuvi monotherapy, was approved for adult patients with r/r DLBCL ineligible for ASCT based on the results from the open-label, multicenter, Phase II single-arm L-MIND study (N=81) (MOR208C203, NCT02399085; Minjuvi SmPC; Duell et al., 2021). Patients received intravenous tafasitamab (12 mg/kg) and oral lenalidomide (25 mg/day on Days 1-21) for up to 12 cycles (28 days each), followed by tafasitamab monotherapy in patients with stable disease or better until disease progression, unacceptable toxicity, or other reasons for discontinuation. The primary endpoint was IRC-assessed ORR per Cheson et al. 2007.

Efficacy results from the 24- and 35-month analyses are presented in the Minjuvi SmPC. For consistency with the data presented in the EPAR, the 24-month analysis is discussed below, though median follow-up was substantially longer for Tafa-Len (31.8 months) than for Glofit-GemOx (22.5 months).

Table 8 summarizes the baseline characteristics of the 81 patients treated with Tafa-Len in L-MIND alongside the 183 patients randomized to Glofit-GemOx in STARGLO (updated analysis).

Table 8. Key baseline characteristics for patients treated with Tafa-Len (L-MIND) or with Glofit-GemOx (ITT, STARGLO)

	Tafa-Len[a] **N=81**	**Glofit-GemOx[b]** **N=183**
Age, median (range), years	72.0 (41-86)	68.0 (22-88)
Age ≥65 years	71.6%	63.4%
Sex, male	54.3%	57.4%
ECOG performance status (PS)		
PS 0	35.8%	40.0%
PS 1	55.6%	49.4%
PS 2	8.6%	10.6%
Histology, DLBCL NOS	87.7%	100%
DLBCL transformed from low-grade lymphoma	9.9%	
Ann Arbor stage III/IV	75.3%	67.2%
Bulky disease (≥7.5 cm)	18.5%	29.0%[c]
IPI score 3-5	50.6%	47.5%
Cell of origin:		
GCB	48.1%	32.8%
ABC/non-GCB	27.2%	56.3%

	Tafa-Len[a] **N=81**	**Glofit-GemOx[b]** **N=183**
Prior therapies, median (range)	2 (1-4)[d]	1 (1-4)
1 prior line	49.4%	62.8%
≥2 prior lines	50.6%	37.2%
Prior ASCT	11.1%	5.5%
Prior CAR T-cell therapy	0	7.1%
Refractory status:		
Last therapy	44.4%	61.2%
Primary-refractory	18.5%[e]	57.9%[f]
Refractory to CAR-T	N/A	7.1%

a Minjuvi EPAR (CCOD 30 November 2019).

b Update CSR GO41944 (STARGLO; CCOD 16 February 2024). Note, 2/183 patients (1.1%) in the Glofit-GemOx arm received Tafa-Len in a prior line.

c Source: t_mh_char_bulk75_IT_16FEB2024_41944.

d Minjuvi SmPC.

e Defined as patients with disease that relapsed or progressed between 3 and 6 months of frontline therapy; these patients were eligible for the study initially. After a protocol amendment (June 2016), patients with primary-refractory disease defined as no response to, or progression during or within 6 months of, frontline therapy were excluded.

f Defined as no response or progression or relapse within 6 months of first anti-lymphoma therapy end date.

The sponsor presented an indirect comparison of efficacy results for patients treated with Tafa-Len in the L-MIND study and those randomized to the Glofit-GemOx arm in the STARGLO study (updated analysis). As previously noted, the median follow-up was substantially longer for the Tafa-Len cohort (31.8 months) than for the Glofit-GemOx cohort (22.5 months), which should be considered when interpreting time-to-event endpoints.

According to the sponsor, Glofit-GemOx showed improved efficacy over Tafa-Len in r/r DLBCL patients in second- and later lines, with higher ORR (BOR: 68.3% vs. 56.8%) and CR rate (BOR: 58.5% vs. 39.5%), despite the STARGLO study including a more refractory population than L-MIND. Median IRC-assessed DOCR and DOR were not reached for Glofit-GemOx, whereas for Tafa-Len, median DOCR was not reached, and median DOR was 34.6 months. At 12 months, event-free rates for DOR were 66.9% for Glofit-GemOx and 76.4% for Tafa-Len (12-month DOCR: 74.4% for Glofit-GemOx; not reported for Tafa-Len).

In addition to higher response rates, Glofit-GemOx showed numerically longer median PFS compared to Tafa-Len (13.8 vs. 12.1 months). However, median OS favoured Tafa-Len over Glofit-GemOx (31.6 vs. 25.5 months, respectively). The higher refractoriness of the Glofit-GemOx population and shorter follow-up time should be considered when comparing OS and PFS across the studies. Furthermore, single-arm studies like L-MIND have inherent limitations, including potential biases and confounding factors due to the lack of a control arm.

Table 9. Key efficacy results for patients treated with Tafa-Len (L-MIND) or with Glofit-GemOx (ITT, STARGLO)

	Tafa-Len[a] **N=81**	**Glofit-GemOx[b]** **N=183**
ORR, % (95% CI)	BOR: 56.8% (45.3, 67.8)	BOR: 68.3% (61.0, 75.0)
CR rate, % (95% CI)	BOR: 39.5% (28.8, 51.0)	BOR: 58.5% (51.0, 65.7)
Median DOCR (95% CI)	NE (43.9, NE)	NE (11.8, NE)
Median DOR (95% CI)	34.6 (26.1, NE)	NE (17.6, NE)
12-month event-free rate	76.4%	66.9%
Median PFS (95% CI)	12.1 (5.7, NE)	13.8 (8.7, 20.5)
Median OS (95% CI)	31.6 (18.3, NE)	25.5 (18.3, NE)
Median OS follow-up (95% CI)	31.8 (27.2, 35.9)	22.5 (20, 24.5)

NE=not evaluable.

a Minjuvi EPAR (CCOD 30 November 2019, median follow-up 31.8 months).

b Update CSR GO41944 (STARGLO; CCOD 16 February 2024, median follow-up 22.5 months).

The sponsor also presented several real-world studies reporting substantially lower response rates and shorter survival for Minjuvi in combination with lenalidomide in a broader transplant-ineligible population in the second- and later-line settings than those reported in the L-MIND study (Table 10).

Table 10. Real-World Evidence of Efficacy of Minjuvi (Tafa-Len)

	L-MIND study **N=81**	**Qualls 2023a** **N=178**	**Paillassa 2023** **N=56**	**Ruckdeschel 2023** **N=127**
ORR	56.8%	31%	33%	33%
CRR	39.5%	19%	29%	12%
Median PFS	11.6 months	1.9 months	not reported	4.7 months
Median OS	31.6 months	6.5 months	3.0 months	8.9 months

Finally, the sponsor provided published data on outcomes with Tafa-Len post-CAR T-cell therapy based on real-world experience. A small retrospective US study using electronic health records indicated lower efficacy of Tafa-Len (Flores Avile et al., 2022) compared to Glofit-GemOx after prior CAR T-cell therapy, as reported in STARGLO (Table 10). This observation was further supported by a retrospective study conducted by Qualls and colleagues (Qualls et al., 2023b), which analysed 178 patients with r/r LBCL treated with Tafa-Len, including 52 patients who had received prior anti-CD19 CAR T-cell therapy (Table 11).

Table 11. Treatment Outcomes with Minjuvi and Columvi after prior CAR-T

	Tafa-Len		**Glofit-GemOx[a]**
	Flores Avile 2022	**Qualls 2023b**	**STARGLO**
	N=8	**N=52**	**N=13**
ORR, %	0%	15%	69.2%
CR rate, %	13%	15%	53.8%
Median PFS	not reported	1.6 months	8.4 months
Median OS	2.3 months	not reported	13.7 months

First therapy given after CAR T cells unless otherwise stated.

a Annex 2 (STARGLO; CCOD 16 February 2024).

Regarding safety, the sponsor emphasised that both Columvi (Glofit-GemOx) and Minjuvi (Tafa-Len) have manageable and acceptable safety profiles in transplant-ineligible patients with r/r DLBCL.

COMP discussion

The COMP concluded that, in general, the efficacy outcomes appeared better in the Glofit-GemOx cohort compared to the Tafa-Len group for most endpoints (point estimates). While the STARGLO study reported significant improvements in ORR and PFS compared to the L-MIND study, the lack of a meaningful OS advantage (25.5 vs. 31.6 months, respectively) raises questions about the clinical relevance of these findings. The selective emphasis on secondary endpoints may overstate the true benefit. In addition, variables such as refractory status were clearly unbalanced across the two groups making it unclear whether one group had a higher disease burden than the other.

Regarding the real-world data presented for Minjuvi, the lack of sufficient background information, including uncertainty quantification (e.g., confidence intervals), limits the interpretability of the findings. Moreover, comparisons of efficacy outcomes across subgroups within clinical studies or across studies is generally considered unreliable. As such, the real-world data provided is insufficient to establish a claim of significant benefit for glofitamab over tafasitamab in patients with r/r DLCBL in the post-CAR-T setting.

Considering the observed imbalances in baseline characteristics, as noted above, the COMP concluded that conducting a MAIC would likely result in a substantially reduced ESS for the adjusted STARGLO population. Nevertheless, it may still be worthwhile to assess the overlap between the populations and evaluate the impact of an adjusted comparison on the treatment effect of glofitamab versus tafasitamab.

Overall COMP conclusion

The claim of significant benefit based on a clinically relevant advantage for glofitamab (Columvi) over the satisfactory methods polatuzumab vedotin (Polivy) and tafasitamab (Minjuvi) in adult patients with r/r DLBCL NOS ineligible for ASCT in second- and later lines is not considered established based on the data provided. The sponsor is therefore requested to provide supplementary data to substantiate the claim of significant benefit for glofitamab over these two products in the target patient population.

4. COMP list of issues

The claim of significant benefit of glofitamab over polatuzumab vedotin (Polivy) and tafasitamab (Minjuvi) for the target patient population is not considered established based on the data presented.

The sponsor should therefore provide additional data to support the claim of significant benefit for glofitamab versus these two products in patients with relapsed or refractory diffuse large B-cell lymphoma not otherwise specified (DLBCL NOS) who are ineligible for autologous stem cell transplant (ASCT). Alternatively, the sponsor could consider indirect comparisons, such as matching-adjusted indirect comparisons versus Polivy and Minjuvi.