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Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Zynlonta (loncastuximab tesirine)
Treatment of diffuse large B-cell lymphoma
EU/3/21/2481

Sponsor: ADC Therapeutics (NL) B.V.

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
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1. Product and administrative information

Product	
Designated active substance	Loncastuximab tesirine
Other name	-
International Non-Proprietary Name	Loncastuximab tesirine
Tradename	Zynlonta
Orphan condition	Treatment of diffuse large B-cell lymphoma
Sponsor's details:	ADC Therapeutics (NL) B.V. Laarderhoogtweg 25 1101 EB Amsterdam Noord-Holland Netherlands
Orphan medicinal product designation procedural history	
Sponsor/applicant	FGK Representative Service GmbH
COMP opinion	15 July 2021
EC decision	20 August 2021
EC registration number	EU/3/21/2481
Post-designation procedural history	
Transfer of sponsorship	Transfer from FGK Representative Service GmbH to ADC Therapeutics (NL) B.V. – EC decision of 7 April 2022
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Sinan B. Sarac / Alexandre Moreau
Applicant	ADC Therapeutics (NL) B.V.
Application submission	6 October 2021
Procedure start	28 October 2021
Procedure number	EMA/H/C/0005685
Invented name	Zynlonta
Proposed therapeutic indication	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. Further information on Zynlonta can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/Zynlonta
CHMP opinion	15 September 2022
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Frauke Naumann-Winter / Maria Elisabeth Kalland
Sponsor's report submission	10 June 2022
COMP discussion and adoption of list of questions	6-8 September 2022
Oral explanation	4 October 2022

COMP opinion	6 October 2022
Appeal to the COMP opinion procedural history	
COMP rapporteur	Elisabeth Johanne Rook / Karri Penttila
Appeal submission	24 October 2022
Appeal oral explanation	8 November 2022
COMP final opinion	10 November 2022

2. Grounds for the COMP opinion

Orphan medicinal product designation

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

"The sponsor FGK Representative Service GmbH submitted on 22 March 2021 an application for designation as an orphan medicinal product to the European Medicines Agency for a medicinal product containing loncastuximab tesirine for treatment of diffuse large B-cell lymphoma (hereinafter referred to as "the condition"). The application was submitted on the basis of Article 3(1)(a) first paragraph of Regulation (EC) No 141/2000 on orphan medicinal products.

Having examined the application, the COMP considered that the sponsor has established the following:

- the intention to treat the condition with the medicinal product containing loncastuximab tesirine was considered justified based on clinical data showing complete responses achieved in patients with disease relapsed and refractory to the second line treatment;
- 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 4.3 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 loncastuximab tesirine will be of significant benefit to those affected by the condition. The sponsor has provided clinical data that demonstrate that patients who relapsed and were refractory to at least two previous lines of therapies responded to treatment with the current 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 loncastuximab tesirine 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's 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).

DLBCL usually arises de novo (primary DLBCL) but can also represent malignant transformation of indolent lymphomas such as follicular lymphoma (FL), marginal zone lymphoma (MZL) or chronic lymphocytic leukaemia/small lymphocytic lymphoma (CLL/SLL), referred to as secondary DLBCL. Hereditary and acquired immunodeficiencies, occupational exposures, and pharmacological immunosuppression in the setting of transplantation or treatment of autoimmune diseases have been identified as factors thought to potentially confer increased risk of developing DLBCL.

The clinical manifestations of DLBCL depend on the site of disease involvement. Patients usually present with a rapidly enlarging tumour mass at single or multiple nodal or extra-nodal sites. The majority of cases occur in the lymph nodes; approximately 40% of patients have extra-nodal involvement. The most common site of extra-nodal involvement is the gastrointestinal tract (stomach, ileocecal region), but DLBCL may occur in any organ/tissue including the bone, testes, spleen, skin, central nervous system (CNS), Waldeyer's ring, salivary gland, thyroid, liver, kidneys, and adrenal glands. Many patients are asymptomatic, but symptoms may occur when tissues or organs are infiltrated. Pain in an enlarged lymph node or organ may be noted if the lymphomatous mass enlarges rapidly and can be associated with B-symptoms (fever, night sweats, weight loss). Other symptoms include pruritus, anorexia, fatigue, pedal oedema (caused by pelvic lymphadenopathy), chest discomfort (caused by mediastinal lymphadenopathy). Additional complications include end-organ damage from disease involvement and myelosuppression leading to infections, anaemia, and thrombocytopenia (Swerdlow et al, 2017; Said, 2013).

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 to include 2 subtypes of DLBCL based on cells of origin (GCB and ABC) as well as recognising co-expression of MYC and BCL2 as double-expressor lymphoma (DEL) (Swerdlow, Blood 2016; 127: 2375-2390). A new category of large B-cell lymphoma (LBCL) called high grade B-cell lymphoma (HGBL) was introduced, which is now recognised as distinct from DLBCL (Sehn et al., 2021; Swerdlow et al., 2016). HGBL comprises two separate subcategories as follows: (1) HGBL with MYC, BCL2, and/or BCL6 translocations, which includes LBCL with MYC, BCL2, and/or BCL6 rearrangements, also known as "double- or triple-hit" lymphomas, and excludes follicular lymphoma or lymphoblastic lymphoma; and 2) HGBL NOS, which includes LBCL that are cytologically "high-grade" and would previously be characterized as B-cell lymphoma unclassifiable, and lack genetic features of double- or triple-hit lymphomas. According to the updated WHO classification of lymphoid neoplasms in 2016, the aggressive B-cell NHL subset LBCL now includes both DLBCL (including DLBCL NOS and other DLBCL subgroups) and HGBL subtypes, in addition to primary mediastinal large B-cell lymphoma (PMBCL). DLBCL accounts for >80% of all cases of LBCL and HGBL accounts for up to 13% of the LBCL cases.

The approved therapeutic indication "*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"* falls within the scope of the designated orphan condition "Treatment of diffuse large B-cell lymphoma".

Intention to diagnose, prevent or treat

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

Chronically debilitating and/or life-threatening nature

The sponsor discussed the severity of the disease and noted that the clinical course of DLBCL can be chronically debilitating due to constitutional symptoms, accompanying lymphadenopathy, end-organ damage from disease involvement, and myelosuppression leading to infections, anaemia and thrombocytopenia.

The sponsor also discussed the life-threatening nature of the disease with approximately 75% of DLBCL patients with advanced stage disease (defined as Ann Arbor Stage III and IV or Stage I and II with associated B-symptoms or bulky disease ≥10 cm). Although the majority of patients (approximately 60%) are cured with immunochemotherapy, 10-15% of patients will be refractory to frontline therapy (no response or relapse within 3 months of therapy), and an additional 20-25% will relapse following initial response to therapy (Sehn and Gascoyne, 2015; Maurer et al, 2014; Patmore et al, 2019). The prognosis of patients whose disease is refractory to initial chemotherapy and who are, therefore, not eligible for autologous stem cell transplant (ASCT), or who relapse early after ASCT is extremely poor, particularly for those who have high risk factors. These patients have a poor response to salvage therapy, with an ORR of 26% (complete response rate [CRR] 7%), and a median survival of approximately 6 months (Crump et al, 2017). Thus, few patients are cured in the salvage setting, and most patients with DLBCL, who are ineligible for ASCT or who relapse after ASCT, have limited treatment options.

The COMP agreed that the clinical course of 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 or refractory (r/r) disease who do not respond to treatment.

Number of people affected or at risk

No sources have been identified by the sponsor where the prevalence is given for DLBCL specifically therefore the sponsor estimated the prevalence using an indirect method based on incidence and disease duration data. For the incidence the sponsor used the incidence of NHL and the percentage of DLBCL from NHL based on literature sources.

The DLBCL prevalence for the 27 European Union member states (EU-27) and the European Economic Area (EEA) was estimated using the formula:

Prevalence (P) = Incidence (I) x Disease Duration (D), where

- Incidence (I) was calculated using a 2-step approach where the known incidence of NHL in the EU/EEA was multiplied by the estimated proportion of NHL which corresponds to DLBCL. Based on the discussions above, the incidence of DLBCL was estimated at 0.6368/ 10,000 using a DLBCL/NHL proportion of 33% (Table 1).

Table 1. Reported DLBCL/NHL proportions and incidence rates considered for the estimation of DLBCL prevalence in EU-27/EEA

	X	Y					
Country	**Population in 2020** (Eurostat, 2021)	**DLBCL /NHL proportion**	**DLBCL incidence rate**	**Reference**	**Type of source**	**Data source/ population coverage**	**Year of data**
Germany	83,166,711	31.4%	0.7	G-BA, 2019	Advisory Report from the Federal Joint Committee (G-BA)	-	2019
France	67,320,216	31.6%	-	Defossez et al, 2019	Surveillance report	23 FRANCIM CRs (covering 22% of French population)	Projection 2018
Italy	59,641,488	35.1%	-	AIRTUM, 2016	Surveillance Report (for DLBCL cases)	AIRTUM CRs (covering 52% of Italian population)	2015
				AIOM-AIRTUM, 2015	Epidemiological report (for NHL cases)		
Spain	47,332,614	32.7%	-	Solans et al, 2019	Peer-reviewed publication	Girona province CR (738,976 inhabitants)	Projection 2020
Poland	37,958,138	33.4%	-	Szumera-Ciećkiewicz et al, 2020	Peer-reviewed publication (for DLBCL cases)	Polish National Cancer registry (covering 100% of Polish population)	2000-2014
				Polish NCR, 2021	Polish National Cancer Registry (for NHL cases)		
Netherlands	17,407,585	35.7%	0.835	Netherlands CR, 2021	Netherlands Cancer Registry	Covers 100% of Netherlands population	2020 (provisional data)
Sweden	10,327,589	37.8%	-	Ekberg et al, 2020	Peer-reviewed publication	Swedish Lymphoma registry (covers 100% of Swedish population)	2008-2016
Adjusted DLBCL /NHL ratio for prevalence estimate#	**323,154,341**	**32.98 %**	Notes: # Calculation algorithm: $Y_1 \times X_1/X_T + Y_2 \times X_2/X_T + \ldots + Y_7 \times X_7/X_T = Y_T$ Underlined values were obtained directly from the literature or based on the number of cases reported in the literature				

- Median Disease Duration (D) was estimated to be 6.78 years, using a 5-year survival of 60%, and assuming a constant hazard rate over the course of survival.

A summary of the point prevalence calculation is presented in Table 2.

Table 2. Prevalence estimates for DLBCL in the EU and EEA

	A	B	C	I	P
Region/ Country	**Population in 2020**	**NHL incidence count for 2020 (ECIS)**	**DLBCL incidence count for 2020 (33% x B)**	**DLBCL incidence rate per 10k per year in 2020 ([C/A]*10,000)**	**DLBCL prevalence per 10k in 2020 (I x 6.78 years)**
EU-27	**447,319,916**	**86,321**	**28,486**	**0.6368**	**4.318**
Norway	5,367,580	1,053			
Iceland	364,134	54			
Liechtenstein	38,747	8*			
EEA	**453,090,377**	**87,436**	**28,854**	**0.6368**	**4.318**

A: Estimated projected EU population from Eurostat database (01 Jan 2020) (https://ec.europa.eu/eurostat/)
B: NHL incident cases for EU-27, Norway, Iceland from ECIS database (https://ecis.jrc.ec.europa.eu/); estimate identical to that from Globocan database (https://gco.iarc.fr)
*Estimated using incident rate of NHL for EU-27+NO+IS (19.3/100,000)

Based on the above, the sponsor concluded on an average prevalence for DLBCL of 4.3 per 10,000 persons in the EU.

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 latest European Society for Medical Oncology (ESMO) guidelines for DLBCL, which describe some of the treatment strategies available to these patients in Europe and outlined the current standard of care in the first- and second-line setting based on the treatment guidelines (Tilly et al., 2015). The sponsor listed all centrally authorised treatment options for DLBCL in table 3, of which the majority of the medicinal products have been authorised in the EU after 2015 and are therefore not included in the current ESMO guidelines.

Table 3. Centrally approved medicinal products for the treatment of DLBCL (April 2022)

Active Substance	**Tradename [MAH]**	**Indication**
Immunotherapeutic agents		
Rituximab	Various	Treatment of adult patients with CD20 positive diffuse large B cell non-Hodgkin's lymphoma in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) chemotherapy.

Active Substance	Tradename [MAH]	Indication
Immunotherapeutic agents		
Polatuzumab vedotin	Polivy [Roche]	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.
Tafasitamab	Minjuvi [Incyte Biosciences]	In combination with lenalidomide followed by Minjuvi monotherapy for the treatment of adult patients with relapsed or refractory DLBCL who are not eligible for autologous stem cell transplant (ASCT)
Axicabtagene ciloleucel	Yescarta [Novartis]	Treatment of adult patients with r/r DLBCL after two or more lines of systemic therapy*. **Note: as of 14 October 2022, Yescarta is indicated for the treatment of adult patients with diffuse large B-cell lymphoma (DLBCL) and high-grade B-cell lymphoma (HGBL) that relapses within 12 months from completion of, or is refractory to, first-line chemoimmunotherapy.*
Tisagenlecleucel	Kymriah [Kite Pharma]	Treatment of adult patients with r/r DLBCL after two or more lines of systemic therapy.
Lisocabtagene maraleucel	Breyanzi [Bristol-Myers Squibb]	Breyanzi is indicated for the treatment of adult patients with relapsed or refractory DLBCL after two or more lines of systemic therapy.

MAH, Marketing Authorisation Holder.

The sponsor also presented in Table 4 the nationally or centrally approved medicinal products used in the treatment of DLBCL (but not specifically authorised for DLBCL).

Table 4. Nationally or centrally approved medicinal products used in the treatment of DLBCL (but not specifically authorised for DLBCL)

Active Substance	Trade name [MAH]	National/ EU Approval	Indication*
Cytotoxic agents			
Bendamustine	*Various*	National	Indolent NHL as monotherapy in patients who have progressed during or within 6 months following treatment with rituximab or a rituximab containing regimen. Also in combination with polatuzumab vedotin and rituximab.
Bleomycin	*Various*	National	Treatment of NHL of intermediate and high malignancy in adults. Bleomycin can be used as a monotherapy, but is usually combined with other cytostatics and/or radiation therapy.
Carboplatin	*Various*	National	Treatment of advanced ovarian carcinoma of epithelial origin in first line therapy, or second line therapy, after other treatments have failed. Treatment of small cell carcinoma of the lung.
Carmustine	Carmustine Obvius [Obvius]	EU	Secondary therapy in non-Hodgkin's lymphoma and Hodgkin's disease. As conditioning treatment prior to autologous haematopoietic progenitor cell transplantation (HPCT) in malignant haematological diseases (Hodgkin's disease / NHL).
	Various	National	Non-Hodgkin's lymphomas – as secondary therapy in combination with other approved drugs in patients who relapse while being treated with primary therapy, or who fail to respond to primary therapy.

Active Substance	Trade name [MAH]	National/ EU Approval	Indication*
Chlorambucil	*Various*	National	Treatment of Hodgkin's disease, certain forms of NHL, chronic lymphocytic leukaemia, and Waldenstrom's macroglobulinaemia.
Cisplatin	*Various*	National	Treatment of advanced or metastasised testicular cancer, ovarian cancer, bladder carcinoma, squamous cell carcinoma of the head and neck, non-small cell lung carcinoma, small cell lung carcinoma. Treatment of cervical carcinoma in combination with other chemotherapeutics or with radiotherapy. Cisplatin can be used as monotherapy and in combination therapy.
Cyclophosphamide	*Various*	National	Treatment of Hodgkin's lymphoma, NHL and Multiple Myeloma. Cyclophosphamide may be used alone or in combination with other chemotherapeutic agents, depending on the indication.
Cytarabine	*Various*	National	For induction of remission in acute myeloid leukaemia in adults and for other acute leukaemias of adults and children.
Docetaxel	*Various*	National	Docetaxel as monotherapy or in combination with other agents is used in: Breast cancer, Non-small cell lung cancer (NSCLC), Prostate cancer, Gastric adenocarcinoma and Head and neck cancer
Doxorubicin	*Various*	National	NHL Doxorubicin is frequently used in combination chemotherapy regimens with other cytotoxic drugs.
Etoposide	*Various*	National	Etoposide injection is indicated in combination with other approved chemotherapeutic agents for the treatment of NHL in adult and paediatric patients.
Gemcitabine	*Various*	National	Treatment of locally advanced or metastatic bladder cancer in combination with cisplatin. Treatment of locally advanced or metastatic adenocarcinoma of the pancreas. Gemcitabine, in combination with cisplatin is indicated as first line treatment of patients with locally advanced or metastatic NSCLC. Gemcitabine monotherapy can be considered in elderly patients or those with performance status 2. Treatment of locally advanced or metastatic epithelial ovarian carcinoma, in combination with carboplatin, in patients with relapsed disease following a recurrence-free interval of at least 6 months after platinum-based, first-line therapy. Gemcitabine, in combination with paclitaxel, is indicated for the treatment of patients with unresectable, locally recurrent or metastatic breast cancer who have relapsed following adjuvant/neoadjuvant chemotherapy. Prior chemotherapy should have included an anthracycline unless clinically contraindicated.
Ifosfamide	*Various*	National	As a single agent ifosfamide has successfully produced objective remissions in a wide range of malignant conditions. Ifosfamide is also frequently used in combination with other cytotoxic drugs, radiotherapy and surgery.
Lomustine	*Various*	National	As second-line treatment in NHL

Active Substance	Trade name [MAH]	National/ EU Approval	Indication*
Melphalan	Phelinun [Adienne]	EU	High-dose of melphalan used alone or in combination with other cytotoxic medicinal products and/or total body irradiation is indicated in the treatment of malignant lymphoma (Hodgkin, non-Hodgkin lymphoma).
	Various	National	Melphalan, at conventional IV dose, is indicated in the treatment of multiple myeloma and advanced ovarian cancer. Melphalan, at high IV dose, is indicated, with or without haematopoietic stem cell transplantation, for the treatment of multiple myeloma and childhood neuroblastoma. Melphalan, administered by regional arterial perfusion, is indicated in the treatment of localised malignant melanoma of the extremities and localised soft tissue sarcoma of the extremities.
Methotrexate	*Various*	National	Methotrexate may be used in combination with other cytotoxic medicinal products for Non-Hodgkin's lymphomas
Oxaliplatin	*Various*	National	Oxaliplatin in combination with 5-fluorouracil (5-FU) and folinic acid (FA) is indicated for: Adjuvant treatment of stage III (Duke's C) colon cancer after complete resection of primary tumour Treatment of metastatic colorectal cancer.
Pixantrone	Pixuvri [Les Laboratoires Servier]	EU	Pixuvri is indicated as monotherapy for the treatment of adult patients with multiply r/r aggressive NHL. The benefit of pixantrone treatment has not been established in patients when used as fifth line or greater chemotherapy in patients who are refractory to last therapy.
Vincristine	*Various*	National	Vincristine sulfate is used either alone or in conjunction with other oncolytic drugs for the treatment of: Malignant lymphomas, including Hodgkin's disease and NHL.
Vindesine	*Various*	National	Vindesine is an anti-neoplastic drug for intravenous use which can be used alone or in combination with other oncolytic drugs.
Glucocorticoids			
Dexamethasone	*Various*	National	Treatment of symptomatic multiple myeloma, acute lymphoblastic leukaemia, Hodgkin's disease and NHL in combination with other medicinal products.
Prednisolone	*Various*	National	Haemolytic anaemia (auto-immune), leukaemia (acute and chronic lymphocytic), lymphoma, multiple myeloma, idiopathic thrombocytopenic purpura.

*Selected indications. When not indicated specifically for NHL, all indications are listed. MAH, Marketing Authorisation Holder.

The sponsor's product loncastuximab tesirine (Zynlonta) is intended to treat adult patients with r/r DLBCL and HGBL after two or more lines of systemic therapy. An overview of medicinal products authorised in the EU for r/r DLBCL and NHL in third- or later lines, and whether they are considered relevant for a discussion on the significant benefit of loncastuximab tesirine in r/r DLBCL and HGBL is given below.

R-CHOP is standard of care in first line treatment, but not used after progression. For younger, high-risk patients, R-CHOEP is a valid option. Patients eligible for Zynlonta are r/r after two or more multi-agent

systemic treatment regimens and therefore for later lines of treatment. There is no need to discuss R-CHOP on significant benefit since Zynlonta only covers patients with r/r disease.

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 Zynlonta is to be used in r/r DLBCL, the therapeutic indications are not considered to be completely overlapping since Zynlonta is intended to be used in the third and later lines while Pixuvri is limited to the third and fourth lines. Therefore, Pixuvri is not considered a satisfactory method for the entire patient population covered by the therapeutic indication for Zynlonta and it should not be discussed under the significant benefit section.

Yescarta (axicabtagene ciloleucel; hereinafter referred to as axi-cel) is approved 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 (*note: as of 14 October 2022, Yescarta is indicated for the treatment of adult patients with diffuse large B-cell lymphoma (DLBCL) and high-grade B-cell lymphoma (HGBL) that relapses within 12 months from completion of, or is refractory to, first-line chemoimmunotherapy)*. Kymriah (tisagenlecleucel; hereinafter referred to as tisa-cel) is indicated for the treatment of adult patients with r/r DLBCL after two or more lines of systemic therapy.

At the time of the simultaneous marketing authorisation of Kymriah and Yescarta, the WHO classification had recently been updated, recognising HGBL as distinct from DLBCL (Swerdlow, Blood 2016; 127: 2375-2390). This separation, however, had not been recognised neither for the enrolment of patients into the pivotal trials for the authorised CAR-T cell products, nor for the purpose of the wording of the approved indications. Patients classified nowadays as HGBL had indeed been included into the pivotal trials for both Yescarta and Kymriah and were also referenced to in their European public assessment reports (EPARs) and in section 5.1 of the SmPC for Yescarta. It was therefore the understanding of the COMP that the reference to DLBCL in the therapeutic indications as stated in section 4.1 of the approved SmPC still covered HGBL for both of these two chimeric antigen receptor (CAR)-T cell products.

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 Zynlonta are not considered to be completely overlapping. Polivy is therefore not considered a satisfactory method for the whole target population for Zynlonta and should not be discussed under the significant benefit section.

Breyanzi (lisocabtagene maraleucel; hereinafter referred to as liso-cel) is indicated for the treatment of adult patients with r/r DLBCL, PMBCL and follicular lymphoma grade 3B (FL3B), after two or more lines of systemic therapy. The target patient population for Breyanzi overlaps with the intended target population for Zynlonta since Breyanzi also covers the HGBL subset (section 5.1 of Breyanzi SmPC) and is therefore considered as a satisfactory method.

Finally, 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 Zynlonta are not considered to be completely overlapping. Minjuvi is

therefore not considered a satisfactory method for the entire target population for Zynlonta and should 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, are considered satisfactory methods relevant for a discussion on the significant benefit of loncastuximab tesirine in r/r DLBCL and HGBL and will be discussed below.

Significant benefit

The sponsor did not ask for protocol assistance for the justification of significant benefit.

The claim of significant benefit is based on the results from the pivotal study for loncastuximab tesirine called LOTIS-2 (also known as ADCT-402-201), which is an open-label, single-arm phase 2 study conducted in 145 adult patients with r/r DLBCL and HGBL after at least 2 prior systemic regimens. The trial excluded patients with bulky disease and active central nervous system lymphoma. Patients received Zynlonta 0.15 mg/kg every 3 weeks for 2 cycles, then 0.075 mg/kg every 3 weeks for subsequent cycles.

Of the 145 patients enrolled, the diagnosis was DLBCL not otherwise specified (NOS) in 88% (including 20% with DLBCL arising from low grade lymphoma) and HGBL in 7%. The median number of prior therapies was 3 (range: 2 to 7). Overall, 43% of the patients received 2 prior therapies, whereas 24% received 3 prior therapies and 32% received more than 3 prior therapies. A total of 63% of the patients had refractory disease, 17% had a pre-treatment history with prior stem cell transplant (SCT), and 9.7% with prior CAR-T cell therapy.

Efficacy was established on the basis of overall response rate (ORR) as assessed by an Independent Review Committee (IRC) using the Lugano 2014 criteria. The primary endpoint of the pivotal study, IRC-assessed ORR, was 48.3% (70/145; 95% CI: 39.9, 56.7), and complete response (CR) was 24.1% (35/145; 95% CI:17.4, 31.9). The median duration of response (DOR) for the responding subjects was 13.37 months (95% CI: 6.87, NE).

The sponsor claimed a SB of Zynlonta in r/r DLBCL and HGBL based on the following arguments:

- Zynlonta (loncastuximab tesirine) versus Yescarta (axi-cel)

The sponsor claimed the significant benefit of loncastuximab tesirine versus axi-cel based on improved safety according to matching adjusted indirect comparisons (MAIC).

Study ADCT-402-201 in loncastuximab tesirine and the ZUMA-1 study in axi-cel differed in their inclusion/exclusion criteria. The ZUMA-1 study (N=101 infused population) limited enrolment to patients who were either (a) refractory to chemotherapy or (b) relapsed within 12 months after ASCT. After application of the necessary inclusion/exclusion criteria from ZUMA-1 to LOTIS-2, only 88 of 145 patients of the patients in LOTIS-2 complied with the ZUMA-1 inclusion/exclusion criteria. After matching, the ESS of the loncastuximab tesirine cohort was further reduced to 54.

All efficacy outcomes considered favoured axi-cel over loncastuximab tesirine, including response rates (ORR difference=-33.4%, 95% CI: -49.1% to -16.6%, p<0.001; CRR difference=-37.3%, 95% CI: 50.8% to -21.8%, p<0.001) (Table 5 and Lonca MAIC Analysis Report, 2022 [MAIC analysis of loncastuximab tesirine vs. CAR-T cell therapies and pixantrone]) and progression-free survival (PFS) and overall survival (OS) (PFS HR=1.92, 95% CI: 1.27 to 2.91, p=0.002; OS HR=2.02, 95% CI: 1.32 to 3.01, p=0.001).

Table 5. MAIC analysis of ORR and CRR for loncastuximab tesirine vs. axi-cel (infused population)

Outcome	Loncastuximab Tesirine		Axi-cel	Risk Difference (95% CI)[1] Loncastuximab Tesirine vs. Axi-cel	
	Before Matching	After Matching		Before Matching	After Matching
ORR (IRC Assessed)	42.0%	40.9%	74.3%	-32.2% (-46.7%, -17.9%)[2]	-33.4% (-49.1%, -16.6%)[2]
CRR (IRC Assessed)	18.2%	17.2%	54.5%	-36.3% (-49.4%, -23.3%)[2]	-37.3% (-50.8%, -21.8%)[2]

Axi-cel = axicabtagene ciloleucel; CI = confidence interval; CRR = complete response rate; IRC = Independent Review Committee; MAIC = matching-adjusted indirect comparison; ORR = overall response rate.
[1]Confidence intervals and p-values for risk difference calculated from bootstrapped samples; p-values calculated assuming a normal distribution.
[2]p<0.001.

Taking into account the 9% of patients who were not infused with axi-cel, in the MAIC analysis using data for the leukapheresed population of the ZUMA-1 study (N=111), the differences in ORR and CRR became slightly smaller, although the direction and statistical significance of treatment effects were the same as those obtained in the analyses using data for the axi-cel infused population (ORR difference= -24.8%, 95% CI: -40.7% to -9.7%, p=0.002; CRR difference=-33.6%, 95% CI: -45.8% to -18.9%, p<0.001).

The sponsor claimed that the MAIC analysis demonstrated a more favourable safety profile of loncastuximab tesirine in comparison to axi-cel, with significantly lower incidence for 18 of the 27 Grade ≥3 TEAEs. The largest differences were for Grade ≥3 anaemia (5.6% vs. 45.4%, p<0.001), decreased neutrophil count (0.0% vs. 32.4%, p<0.001), decreased platelet counts (0.0% vs. 29.6%, p<0.001), and febrile neutropenia (1.4% vs. 32.4%, p<0.001). Grade ≥3 increased gamma-glutamyltransferase (GGT) was the only statistically significant Grade ≥3 TEAE for which the incidence was greater for loncastuximab tesirine vs. axi-cel (22.4% vs. 0.0%, p<0.001) (Table 6).

Table 6. MAIC analysis of safety outcomes for loncastuximab tesirine vs. axi-cel (infused population)

	% Patients with TEAE				
	Loncastuximab Tesirine			Risk Difference (95% CI)[1] Loncastuximab Tesirine vs. Axi-cel	
Outcome	Before Matching	After Matching	Axi-cel	Before Matching	After Matching
Any TEAE Grade ≥3	65.9%	69.1%	98.1%	-32.2% (-42.2%, -22.8%)[2]	-29.1% (-41.2%, -17.4%)[2]
Anaemia	5.7%	5.6%	45.4%	-39.7% (-50.2%, -27.9%)[2]	-39.7% (-50.5%, -27.8%)[2]
Aphasia	0.0%	0.0%	7.4%	-7.4% (-12.0%, -2.8%)[3]	-7.4% (-12.0%, -2.8%)[3]
Confused state	1.1%	0.4%	9.3%	-8.1% (-13.9%, -2.4%)[3]	-8.9% (-14.8%, -3.7%)[3]
Cytokine release syndrome	0.0%	0.0%	11.1%	-11.1% (-17.6%, -5.6%)[2]	-11.1% (-17.6%, -5.6%)[2]
Diarrhoea	0.0%	0.0%	4.6%	-4.6% (-8.3%, -0.9%)[4]	-4.6% (-8.3%, -0.9%)[4]
Encephalopathy	0.0%	0.0%	23.1%	-23.1% (-31.0%, -15.7%)[2]	-23.1% (-31.0%, -15.7%)[2]
Febrile neutropenia	2.3%	1.4%	32.4%	-30.1% (-39.4%, -20.3%)[2]	-31.1% (-39.9%, -21.7%)[2]

GGT increased	19.3%	22.4%	0.0%	19.3% (11.4%, 28.4%)[2]	22.4% (13.1%, 34.3%)[2]
Hyperglycaemia	0.0%	0.0%	4.6%	-4.6% (-8.3%, -0.9%)[4]	-4.6% (-8.3%, -0.9%)[4]
Hypertension	2.3%	1.7%	7.4%	-5.1% (-10.9%, 0.5%)	-5.7% (-11.1%, -0.4%)[4]
Hypocalcaemia	0.0%	0.0%	6.5%	-6.5% (-11.1%, -2.8%)[3]	-6.5% (-11.1%, -2.8%)[3]
Hyponatremia	2.3%	1.9%	11.1%	-8.8% (-15.5%, -2.3%)[3]	-9.2% (-15.9%, -2.8%)[3]
Hypophosphatemia	2.3%	2.5%	18.5%	-16.2% (-24.1%, -8.2%)[2]	-16.1% (-24.2%, -7.4%)[2]
Hypotension	0.0%	0.0%	13.9%	-13.9% (-20.4%, -7.4%)[2]	-13.9% (-20.4%, -7.4%)[2]
Hypoxia	0.0%	0.0%	11.1%	-11.1% (-17.6%, -5.6%)[2]	-11.1% (-17.6%, -5.6%)[2]
Increased alanine aminotransferase	3.4%	3.7%	5.6%	-2.1% (-8.1%, 3.4%)	-1.8% (-8.2%, 4.5%)
Increased aspartate aminotransferase	1.1%	1.4%	6.5%	-5.3% (-10.8%, -0.5%)[4]	-5.1% (-10.6%, 0.1%)
Leukopenia	6.8%	8.8%	16.7%	-9.8% (-18.6%, -0.9%)[4]	-7.9% (-17.6%, 2.8%)
Lymphopenia	1.1%	1.7%	0.0%	1.1% (0.0%, 3.4%)	1.7% (0.0%, 5.6%)
Lymphocyte count decreased	0.0%	0.0%	20.4%	-20.4% (-27.8%, -13.0%)[2]	-20.4% (-27.8%, -13.0%)[2]
Neutropenia	19.3%	23.1%	38.9%	-19.6% (-31.5%, -7.2%)[3]	-15.8% (-29.5%, -1.3%)[4]
Neutrophil count decreased	0.0%	0.0%	32.4%	-32.4% (-40.7%, -23.1%)[2]	-32.4% (-40.7%, -23.1%)[2]
Platelet count decreased	0.0%	0.0%	29.6%	-29.6% (-38.0%, -20.4%)[2]	-29.6% (-38.0%, -20.4%)[2]
Pyrexia	1.1%	1.0%	13.9%	-12.8% (-20.1%, -6.3%)[2]	-12.9% (-20.3%, -6.4%)[2]
Somnolence	0.0%	0.0%	8.3%	-8.3% (-13.0%, -3.7%)[3]	-8.3% (-13.0%, -3.7%)[3]
Thrombocytopenia	15.9%	20.3%	24.1%	-8.2% (-18.9%, 3.3%)	-3.7% (-16.2%, 10.5%)
White blood cell count decreased	0.0%	0.0%	28.7%	-28.7% (-37.0%, -20.4%)[2]	-28.7% (-37.0%, -20.4%)[2]

Axi-cel, axicabtagene ciloleucel; CI, confidence interval; GGT, Gamma-glutamyltransferase; MAIC, matching-adjusted indirect comparison; TEAE, treatment-emergent adverse event.

1. ZUMA-1 trial reported long-term adverse event counts including 7 patients in the Phase 1 trial, leading to a total of 108 patients instead of 101. Weighting was conducted separately using reported baseline characteristics for combined Phase 1 and Phase 2 patients. Confidence intervals and p-values for risk difference calculated from bootstrapped samples; p-values calculated assuming a normal distribution.

2. $p<0.001$.

3. $p<0.01$.

4. $p<0.05$.

In conclusion, the sponsor claimed that the results of the MAIC analysis suggest that, in patients with r/r DLBCL and HGBL, loncastuximab tesirine is likely to have a generally more favourable safety profile than axi-cel. There is no observed risk for cytokine release syndrome (CRS), and the largest statistically significant differences in favour of loncastuximab tesirine included any Grade ≥3 TEAE and

(all Grade ≥3) anaemia, decreased platelet count and decreased neutrophil count, neutropenia, and febrile neutropenia.

The COMP considered that given the limited experience with Zynlonta thus far, the claim of better safety in comparison to Yescarta cannot be concluded on at present stage and cannot be quantified in the setting of an indirect comparison where confounding by indication and selection bias cannot be assessed.

In addition, the efficacy of loncastuximab tesirine was shown to be inferior compared to axi-cel in the MAIC. While the difference in efficacy outcomes is less when the analysis is based on the enrolled or leukapheresed population, the CAR-T cell product still appears to provide more benefit to the target patient population. The reduced benefit reflects the logistical challenge of providing CAR-T cell therapies to all patients who may qualify for this treatment option. In addition to the possible safety benefit with loncastuximab tesirine, a potential major contribution to patient care was highlighted by the sponsor since that treatment requires no bridging- or pre-treatment therapy and can be used in all centres specialised in treating oncology patients. Additionally, it can be provided without delay to patients suffering from a highly aggressive disease.

Regarding efficacy, the sponsor should present the efficacy results from the 9.7% of patients who received prior CAR-T cell therapy in the pivotal study LOTIS-2 for Zynlonta and provide more details of the type of CAR-T cell therapies that they received.

- Zynlonta (loncastuximab tesirine) versus Kymriah (tisa-cel)

The sponsor claimed the significant benefit of loncastuximab tesirine versus tisa-cel based on improved safety according to MAIC.

Based on the inclusion/exclusion criteria of the JULIET study (also known as study C2201; N=115 infused population), data from 37 patients in LOTIS-2 were excluded, since only 108 of 145 of the patients in LOTIS-2 complied with the JULIET inclusion/exclusion criteria. After matching, the effective sample size (ESS) of the loncastuximab tesirine cohort was further reduced to 56.

There were no statistically significant differences between loncastuximab tesirine and tisa-cel in any of the efficacy outcomes compared (ORR: 51.7% vs 53.0%, difference=-1.4%, 95% confidence interval [CI]: -17.0% to 15.0%; CRR: 25.2% vs 39.1%, difference= -13.9%, 95% CI: -27.9% to 0.1%) (Table 7 and Lonca MAIC Analysis Report, 2022 [MAIC analysis of loncastuximab tesirine vs. CAR-T cell therapies and pixantrone]). Similar observations were made for PFS and OS (PFS hazard ratio [HR]=0.87, 95% CI: 0.55 to 1.38; OS HR=1.11, 95% CI: 0.73 to 1.71).

Table 7. MAIC analysis of ORR and CRR for loncastuximab tesirine vs. tisa-cel (infused population)

	Loncastuximab Tesirine			**Risk Difference (95% CI)[1]** **Loncastuximab Tesirine vs. Tisa-cel**	
Outcome	**Before Matching**	**After Matching**	**Tisa-cel**	**Before Matching**	**After Matching**
ORR (IRC Assessed)	50.0%	51.7%	53.0%	-3.0% (-16.0%, 10.5%)	-1.4% (-17.0%, 15.0%)
CRR	25.9%	25.2%	39.1%	-13.2%	-13.9%

	Loncastuximab Tesirine			Risk Difference (95% CI)[1] Loncastuximab Tesirine vs. Tisa-cel	
Outcome	**Before Matching**	**After Matching**	**Tisa-cel**	**Before Matching**	**After Matching**
(IRC Assessed)				(-25.5%, -0.4%)[2]	(-27.9%, 0.1%)

CI, confidence interval; CRR, complete response rate; IRC, Independent Review Committee; MAIC, matching-adjusted indirect comparison; ORR, overall response rate; tisa-cel, tisagenlecleucel.

1. Confidence intervals and p-values for risk difference calculated from bootstrapped samples; p-values calculated assuming a normal distribution.
2. $p<0.05$.

The sponsor claimed that the results of the MAIC analysis suggest that, in patients with r/r DLBCL and HGBL, loncastuximab tesirine is likely to have a generally more favourable safety profile than tisa-cel. There is no observed risk for CRS, and the largest statistically significant differences in favour of loncastuximab tesirine included any Grade ≥3 TEAE and (all Grade ≥3) anaemia, decreased platelet count, decreased neutrophil count, febrile neutropenia and decreased white blood cell count (Table 8).

Table 8. MAIC analysis of safety outcomes for loncastuximab tesirine vs. tisa-cel (infused population)

	% Patients with TEAE				
	Loncastuximab Tesirine			Risk Difference (95% CI)[1] Loncastuximab Tesirine vs. Tisa-cel	
Outcome	**Before Matching**	**After Matching**	**Tisa-cel**	**Before Matching**	**After Matching**
Any TEAE Grade ≥3	71.3%	76.6%	90.4%	-19.1% (-29.1%, -9.2%)[2]	-13.8% (-25.4%, -3.1%)[3]
Anaemia	7.4%	5.9%	39.1%	-31.7% (-41.5%, -22.0%)[2]	-33.2% (-42.5%, -23.4%)[2]
Cytokine release syndrome	0.0%	0.0%	22.6%	-22.6% (-30.4%, -14.8%)[2]	-22.6% (-30.4%, -14.8%)[2]
Fatigue	1.9%	1.1%	6.1%	-4.2% (-9.5%, 0.3%)	-4.9% (-9.9%, -0.6%)[3]
Febrile neutropenia	2.8%	1.4%	16.5%	-13.7% (-20.9%, -6.5%)[2]	-15.1% (-22.0%, -7.9%)[2]
GGT increased	19.4%	28.3%	0.0%	19.4% (12.0%, 26.9%)[2]	28.3% (15.5%, 40.7%)[2]
Hypokalaemia	2.8%	3.2%	8.7%	-5.9% (-11.3%, 0.3%)	-5.5% (-11.3%, 1.0%)
Hypophosphatemia	3.7%	1.8%	13.0%	-9.3% (-16.4%, -2.2%)[4]	-11.2% (-17.3%, -4.3%)[2]
Hypotension	0.9%	0.2%	8.7%	-7.8% (-13.0%, -2.5%)[4]	-8.5% (-13.7%, -3.4%)[4]
Acute kidney injury	0.9%	0.9%	5.2%	-4.3% (-8.7%, 0.1%)	-4.3% (-8.7%, 0.0%)
Leukopenia	2.8%	1.8%	0.0%	2.8% (0.0%, 6.5%)	1.8% (0.0%, 4.4%)
Lymphopenia	7.4%	8.6%	0.0%	7.4% (2.8%, 13.0%)[4]	8.6% (2.4%, 17.0%)[3]
Neutropenia	24.1%	25.2%	20.0%	4.1% (-6.4%, 15.3%)	5.2% (-7.6%, 18.3%)
Neutrophil count decreased	0.0%	0.0%	32.2%	-32.2% (-40.9%, -23.5%)[2]	-32.2% (-40.9%, -23.5%)[2]

Platelet count decreased	0.0%	0.0%	27.0%	-27.0% (-34.8%, -18.3%)[2]	-27.0% (-34.8%, -18.3%)[2]
Pneumonia	0.9%	0.3%	7.8%	-6.9% (-12.1%, -1.7%)[3]	-7.6% (-12.2%, -3.0%)[4]
Pyrexia	0.9%	1.7%	5.2%	-4.3% (-8.7%, -0.3%)[3]	-3.5% (-8.7%, 1.5%)
Thrombocytopenia	14.8%	13.6%	12.2%	2.6% (-5.7%, 11.0%)	1.5% (-7.8%, 10.9%)
White blood cell count decreased	0.0%	0.0%	29.6%	-29.6% (-37.4%, -20.9%)[2]	-29.6% (-37.4%, -20.9%)[2]

CI, confidence interval; GGT, Gamma-glutamyltransferase; MAIC, matching-adjusted indirect comparison; TEAE, treatment-emergent adverse event; tisa-cel, tisagenlecleucel.

1. Confidence intervals and p-values for risk difference calculated from bootstrapped samples; p-values calculated assuming a normal distribution.
2. p<0.001.
3. p<0.05.
4. p<0.01.

In addition, the sponsor claimed that the efficacy of loncastuximab tesirine may be similar to that of tisa-cel. The same arguments as above regarding the availability of the CAR-T cell products have been used by the sponsor.

The COMP considered that given the limited experience with Zynlonta 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. Regarding efficacy, the sponsor should present the efficacy results from the 9.7% of patients who received prior CAR-T cell therapy in the pivotal study LOTIS-2 for Zynlonta and provide more details of the type of CAR-T cell therapies that they received.

- Zynlonta (loncastuximab tesirine) versus Breyanzi (liso-cel)

The sponsor claimed the significant benefit of loncastuximab tesirine versus liso-cel based on improved safety according to MAIC.

Although the results of a phase 2 study of liso-cel in 46 patients with r/r aggressive B-cell NHL (NCT03484702; TRANSCENDWORLD) were included in the EMA assessment of the marketing authorisation application for Breyanzi, this study was not included in the analysis because these data were published in January 2022, which was after the literature search was conducted for the MAIC analysis (October 2021).

The MAIC analysis included the data from TRANSCEND study (NCT02631044) (N=269 infused population receiving conforming liso-cel, N=256 efficacy population). Data from 19 patients in LOTIS-2 were excluded, reducing the sample size for loncastuximab tesirine from 145 to 126 patients. After matching, the ESS for loncastuximab tesirine cohort was further reduced to 50.

The ORR and CRR statistically favoured liso-cel over loncastuximab tesirine (ORR difference= -28.3%, 95% CI: -42.0% to -13.3%, p<0.001; CRR difference=-28.3%, 95% CI: -40.9% to -13.3%, p<0.001) (Table 9). Although PFS and OS also were numerically greater for liso-cel, treatment effects on these outcomes were statistically significant only for OS (PFS HR=1.28, 95% CI: 0.82 to 2.01, p=0.284; OS HR=1.55, 95% CI: 1.07 to 2.25, p=0.021).

Table 9. MAIC analysis of ORR and CRR for loncastuximab tesirine vs. liso-cel (infused population)

	Loncastuximab Tesirine			Risk Difference (95% CI)[1] Loncastuximab Tesirine vs. Liso-cel	
Outcome	**Before Matching**	**After Matching**	**Liso-cel**	**Before Matching**	**After Matching**
ORR (IRC Assessed)	47.6%	44.4%	72.7%	-25.0% (-35.5%, -15.6%)[2]	-28.3% (-42.0%, -13.3%)[2]
CRR (IRC Assessed)	25.4%	24.8%	53.1%	-27.7% (-37.6%, -18.6%)[2]	-28.3% (-40.9%, -13.3%)[2]

CI. confidence interval; CRR, complete response rate; IRC, Independent Review Committee; Liso-cel, lisocabtagene maraleucel; MAIC, matching-adjusted indirect comparison; ORR. Overall response rate.

[1]Confidence intervals and p-values for risk difference calculated from bootstrapped samples; p-values calculated assuming a normal distribution.

[2]p<0.001.

In the MAIC analysis using data for the leukapheresed population of the TRANSCEND study (N=345), differences in response rates and OS were smaller, though the results still statistically favoured liso-cel (ORR difference=-21.6%, 95% CI: -33.0% to -8.1%, p=0.001; CRR difference= -21.6%, 95% CI: -31.6% to -10.4%, p<0.001; OS HR=1.40, 95% CI: 1.02 to 1.93, p=0.039).

Loncastuximab tesirine had statistically significantly lower incidences of Grade ≥3 anaemia (15.6% vs. 37.5%, p=0.001), febrile neutropenia (2.6% vs. 8.9%, p=0.001), and neutropenia (25.6% vs. 59.9%, p<0.001) (Table 10). Grade ≥3 increased GGT was greater with loncastuximab tesirine vs. liso-cel (19.3% vs. 0.0%, p<0.001).

Table 10. MAIC analysis of safety outcomes for loncastuximab tesirine vs. liso-cel (infused population)

	% Patients with TEAE				
	Loncastuximab Tesirine			Risk Difference (95% CI)[1] Loncastuximab Tesirine vs. Liso-cel	
Outcome	**Before Matching**	**After Matching**	**Liso-cel**	**Before Matching**	**After Matching**
Any TEAE Grade ≥3	72.2%	67.4%	79.2%	-7.0% (-16.3%, 2.1%)	-11.8% (-26.1%, 1.9%)
Anaemia	9.5%	15.6%	37.5%	-28.0% (-35.4%, -20.1%)[2]	-22.0% (-34.4%, -7.2%)[4]
Encephalopathy	0.0%	0.0%	6.7%	-6.7% (-9.7%, -3.7%)[2]	-6.7% (-9.7%, -3.7%)[2]
Febrile neutropenia	3.2%	2.6%	8.9%	-5.7% (-10.4%, -1.1%)[3]	-6.3% (-10.8%, -1.3%)[4]
GGT increased	19.0%	19.3%	0.0%	19.0% (12.7%, 26.6%)[2]	19.3% (9.0%, 31.9%)[2]
Hypertension	2.4%	2.4%	4.5%	-2.1% (-5.9%, 1.8%)	-2.1% (-5.9%, 2.1%)
Hypophosphatemia	4.8%	8.6%	5.9%	-1.2% (-5.9%, 3.5%)	2.7% (-6.4%, 15.9%)
Leukopenia	7.1%	13.4%	14.5%	-7.4% (-13.6%, -1.3%)[3]	-1.1% (-13.0%, 12.5%)
Lymphopenia	4.0%	9.5%	2.6%	1.4% (-2.5%, 5.6%)	6.9% (-2.4%, 20.3%)
Neutropenia	23.8%	25.6%	59.9%	-36.0% (-44.9%, -26.1%)[2]	-34.2% (-47.1%, -20.1%)[2]

	% Patients with TEAE				
	Loncastuximab Tesirine			Risk Difference (95% CI)[1] Loncastuximab Tesirine vs. Liso-cel	
Outcome	**Before Matching**	**After Matching**	**Liso-cel**	**Before Matching**	**After Matching**
Thrombocytopenia	16.7%	24.7%	26.8%	-10.1% (-18.6%, -2.1%)[3]	-2.1% (-15.9%, 12.1%)

CI, confidence interval; GGT, gamma-glutamyltransferase; Liso cel, lisocabtagene maraleucel; MAIC, matching-adjusted indirect comparison; TEAE, treatment emergent adverse event.

[1]Confidence intervals and p-values for risk difference calculated from bootstrapped samples; p-values calculated assuming a normal distribution

[2]p<0.001.

[3]p<0.05.

[4]p<0.01.

In conclusion, the sponsor claimed that the results of the MAIC analysis suggest that, in patients with r/r DLBCL and HGBL, loncastuximab tesirine is likely to have a generally more favourable safety profile than liso-cel. There is no observed risk for CRS, and the largest statistically significant differences in favour of loncastuximab tesirine included (all Grade ≥3) anaemia, neutropenia, and febrile neutropenia.

In addition, the efficacy of loncastuximab tesirine is likely to be less than that of liso-cel in patients with r/r DLBCL and HGBL. The same arguments as above regarding the availability of the CAR-T cell products have been used by the sponsor.

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

Regarding the claim of significant benefit, the sponsor was requested to present the efficacy results from the 9.7% of patients who received prior CAR-T cell therapy in the pivotal study LOTIS-2 for Zynlonta and provide more details of the type of CAR-T cell therapies that they received.

4. COMP list of issues

Significant benefit of loncastuximab tesirine over the approved CAR-T cell products for the target patient population, tisa-cel (Kymriah), axi-cel (Yescarta) and liso-cel (Breyanzi) is not considered established based on the data presented. The sponsor should specifically provide more information on the subset of patients who had been pre-treated with the approved CAR-T cell therapies with regards to:

- disease status at the time of the CAR-T cell treatment (relapse or refractory disease),
- the best response and duration of response as achieved with treatment with Zynlonta reported for each subgroup of patients who were pre-treated with the individual CAR-T cell therapies separately.

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

The sponsor has presented more data from the 14 patients (9.7%; 14/145) in the pivotal study LOTIS-2 who had previously received CAR-T cell therapy before study entry as requested to further justify the claim for significant benefit of loncastuximab tesirine over tisa-cel, axi-cel, and liso-cel in the third- and later lines setting for the target patient population. In addition, data from those patients who had not been treated with any CAR-T cell product prior to study entry was provided for comparison with the subset of patients who were pre-treated with this class of therapy.

The sponsor has provided - based on a data cut-off (DCO) date of 01/Mar/2022 - the best responses for each of the 14 patients: (i) to prior anticancer therapies immediately before infusion with the CAR-T cell therapies; (ii) to the CAR-T cell therapies administered and to (iii) Zynlonta. Nine of these patients had progressed after CAR-T cell therapy, four patients were refractory to this treatment, and for one patient this information was not available.

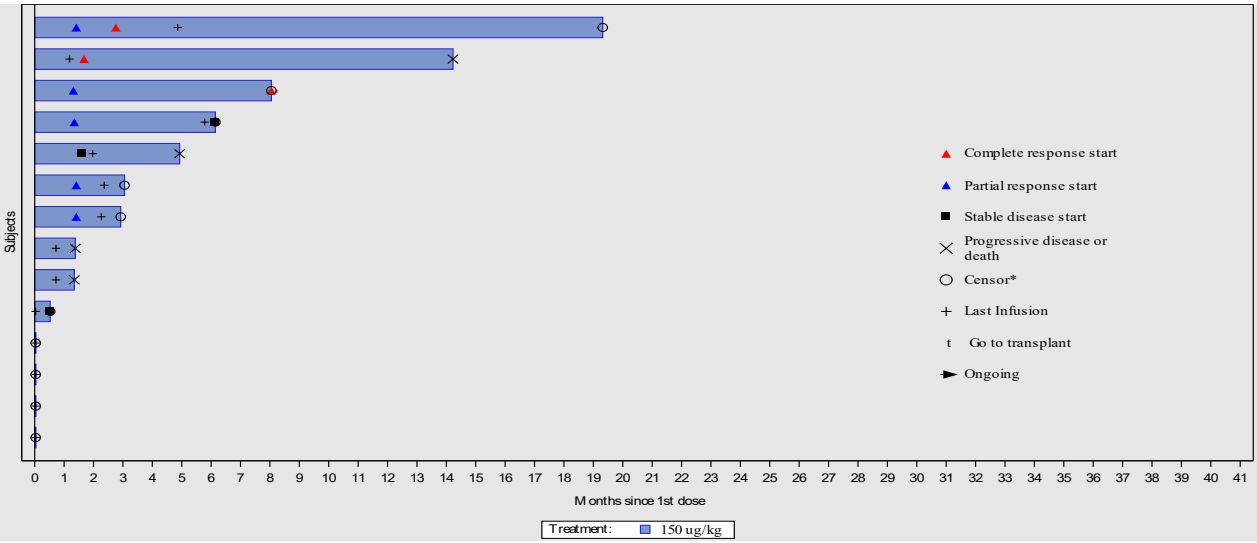
The ORR and CRR achieved in patients who had or had not received CAR-T cell therapies prior to Zynlonta treatment are presented in Table 11. The study protocol did not require information of the type of prior CAR-T cell therapy to be captured in the clinical database, and hence the type of CAR-T cell therapy was not available for 6 patients (42.9%; 6/14). For the remaining 8 patients, 7 patients received axi-cel, and one patient received liso-cel as prior therapy. Of the three patients who achieved CR after Zynlonta treatment, one patient received axi-cel, and two received CAR-T cell products without further specification. Of the three patients who had PR after Zynlonta treatment, one received axi-cel, one received liso-cel, and the other received CAR-T cell therapy without any further specification by the site in the clinical database. The median DOR was 13.37 months (95% CI: 5.98, NR) in patients without prior CAR-T cell therapy and not estimable in patients with prior CAR-T cell therapy due to the small sample size and the very limited follow-up in the majority of the patients (see swimmer plot, Figure 1).

Table 11. LOTIS-2: ORR by Independent Reviewer by Use of Prior CAR-T cell Therapy

	Use of Prior CAR-T Therapy		**All-Treated Population (N=145)**
	Yes (N=14)	**No (N=131)**	
Best Overall Response			
Complete response	3 (21.4)	33 (25.2)	36 (24.8)
Partial response	3 (21.4)	31 (23.7)	34 (23.4)
Stable disease	2 (14.3)	20 (15.3)	22 (15.2)
Not evaluable	4 (28.6)	19 (14.5)	23 (15.9)
Progressive disease	2 (14.3)	28 (21.4)	30 (20.7)
ORR (CR + PR)	6 (42.9)	64 (48.9)	70 (48.3)
95% CI for ORR	(17.7, 71.1)	(40.0, 57.5)	(39.9, 56.7)
95% CI for CR	(4.7, 50.8)	(18.0, 33.8)	(18.0, 32.7)

CI=confidence interval, CR=complete response, ORR=overall response rate, PR=partial response
Note: Best overall response by independent reviewer. Not evaluable included patients without any scan to the independent reviewer (even clinical progressive disease) or patients whose scan was determined to be not evaluable by the independent reviewer.

Figure 1. LOTIS2: Individual anti-tumor responses in patients who had failed prior CAR-T therapies



Abbreviations: CR=complete response, NA=not available, NE=not evaluable, PD=progressive disease, PR=partial response, SD=stable disease

The sponsor concluded that although the number of patients who had received prior CAR-T cell therapies in the pivotal study LOTIS-2 is small, the anti-tumour activity is comparable between patients who had failed (relapsed after/refractory to) prior CAR-T cell therapies and patients who had not received prior CAR-T cell therapies before study entry. Therefore, in the opinion of the sponsor, patients who had failed prior CAR-T cell therapies could still be successfully treated with Zynlonta, as shown by the clinical response rates observed, even though both therapeutics target the B-cell specific surface marker CD19. Zynlonta could therefore, in the opinion of the sponsor, offer an important treatment option for patients with r/r DLBCL and HGBL who have failed prior CAR-T cell therapy.

The COMP agreed that the data provided from the 14 patients in the pivotal study LOTIS-2 (DCO: 1 March 2022) who had previously received CAR-T cell therapy before study entry indicated that loncastuximab tesirine may offer benefit for these patients since they achieved an ORR of 42.9% (6/14; 95% CI: 17.7, 71.1), whereas those who had not been treated with any CAR-T cell product prior to study entry had an ORR of 48.9% (64/131; 95% CI: 40.0, 57.5). However, the median DOR was not estimable in patients with prior CAR-T cell therapy due to the small sample size, and the confidence interval for the observed ORR in these patients was also rather wide.

In general, the response rate alone is not considered sufficient to conclude on any beneficial effect and the information on the durability of the observed responses was regarded as too limited for at least 9 of the 14 patients. In addition, the prior treatment was not known to comprise all the three approved CAR-T cell products constituting the satisfactory methods. In particular, only two of the 7 patients who previously received axi-cel were reported to have achieved a response to loncastuximab tesirine (one had a CR and the other a PR). Both patients had relapsed after prior treatment with axi-cel. The patient who was recorded to have relapsed after prior treatment with liso-cel obtained a PR to loncastuximab tesirine. In addition, none of the patients for whom the type of prior CAR-T cell therapy received were reported had received tisa-cel.

In view of the uncertainties associated with the clinical relevance of the treatment of patients with relapsed disease after CAR-T cell therapy, the statistically significant lower efficacy in the setting of the MAICs still remain. Therefore, the COMP considers that the data provided does not allow a positive conclusion on the equivalence of loncastuximab tesirine versus the authorised CAR-T cell therapies

Yescarta and Breyanzi in terms of efficacy. With regard to Yescarta (axi-cel), loncastuximab tesirine is inferior, at least in terms of survival. With regard to liso-cel (Breyanzi), loncastuximab tesirine is inferior in terms of ORR and CRR. Furthermore, the results for PFS and OS do not look favourable. With regards to tisa-cel (Kymriah), the COMP noted the absence of statistically significant differences with respect to efficacy.

The COMP considered that given the limited experience with Zynlonta thus far, the claim of better safety in comparison to Yescarta, Kymriah, and Breyanzi cannot be concluded on at present stage and cannot be quantified in the setting of an indirect comparison where confounding by indication and selection bias cannot be assessed. Therefore, the clinical relevance of the observed different toxicity profile cannot be judged, especially in the absence of objective criteria for selecting salvage therapy. On balance, the COMP considered that there is no conclusive evidence on which to establish the claim of better safety of Zynlonta over the satisfactory methods of treatment.

Regarding the sponsors' argument that treatment with loncastuximab tesirine 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, the COMP acknowledged it. 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, i.e., in this case tisa-cel, axi-cel, and liso-cel. Reference is made, in this respect, to the 2016 "*Commission notice on the application of Articles 3, 5 and 7 of Regulation (EC) No 141/2000 on orphan medicinal products*" (available at:

https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=OJ:JOC_2016_424_R_0003&from=EN).

Based on the data provided by the sponsor, a positive conclusion on the product's (loncastuximab tesirine) equivalence in terms of efficacy, safety, and benefit/risk balance vis a vis the authorised products versus axi-cel (Yescarta), tisa-cel (Kymriah), and liso-cel (Breyanzi) cannot be drawn. In turn, a claim of major contribution to patient care cannot be established.

In conclusion, the COMP is of the opinion that the data presented by the sponsor does not allow a positive conclusion on the significant benefit of loncastuximab tesirine versus axi-cel (Yescarta), tisa-cel (Kymriah), and liso-cel (Breyanzi).

5. COMP position adopted on 6 October 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;
- the sponsor's claim that Zynlonta is of significant benefit to those affected by the orphan condition does not hold since the sponsor could not establish the existence of a clinically relevant advantage over Yescarta, Kymriah and Breyanzi which are authorised satisfactory methods of treatment.
  - A different safety profile of Zynlonta compared to the approved CAR-T cell products cannot be concluded as being better based on the limited experience with Zynlonta and in the setting of an indirect comparison where confounding by indication and selection bias cannot be excluded.
  - In addition, matching-adjusted indirect comparisons between the patient populations from the pivotal trials for Zynlonta and the approved CAR-T cell products, which were considered as satisfactory methods of treatment for the target patient population, showed a statistically significant inferior efficacy of Zynlonta in comparison to Yescarta and Breyanzi.
  - The data on individual patients failing prior treatment with CAR-T cell therapy before study entry were considered inconclusive in view of the overall low number of patients in this subset, limited information on the type of treatment received and with limited follow-up, so that the clinical relevance of responses could not be reliably determined.
  - Furthermore, the claim for major contribution to patient care cannot be accepted when the efficacy is not established as being comparative.

The data submitted did not allow the COMP to conclude that the claim for significant benefit of loncastuximab tesirine over the satisfactory methods of treatment for adult patients with relapsed or refractory DLBCL and HGBL in the third- and later lines setting has been appropriately demonstrated.

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 not satisfied.

The Committee for Orphan Medicinal Products has recommended that Zynlonta, loncastuximab tesirine for treatment of diffuse large B-cell lymphoma (EU/3/21/2481) is removed from the Community Register of Orphan Medicinal Products.

6. Appeal to the negative opinion adopted on 6 October 2022

Grounds for appeal

The sponsor presented detailed grounds for appeal (EMA/OD/0000115078) on 24 October 2022.

The detailed grounds for appeal were further addressed by the sponsor at an oral explanation before the COMP on 8 November 2022.

Comments on the grounds of appeal

The data submitted by the sponsor previously did not allow the COMP to conclude that the claim for significant benefit of loncastuximab tesirine (Zynlonta) over the satisfactory methods of treatment for adult patients with r/r DLBCL and HGBL in the third- and later-line setting (i.e. the CAR-T cell products Yescarta, Kymriah, Breyanzi) has been appropriately demonstrated. For ease of reference, these three products (namely, the satisfactory methods of treatment), will be referred to collectively in this Report as CAR-T cell products or CAR-T cell therapy/therapies.

In particular, the sponsor had submitted in the context of the initial review a claim of clinically relevant advantage (specifically, better safety) and a claim of major contribution to patient care (the latter based on the arguments that treatment with Zynlonta requires no bridging- or pre-treatment therapy; that Zynlonta can be used in all centres specialised in treating oncology patients; and that Zynlonta can be provided without delay to patients suffering from a highly aggressive disease).

It bears recalling that the claim of major contribution to patient care may only be granted if the sponsor first establishes the equivalence in terms of efficacy and safety between the candidate orphan products and the satisfactory methods of treatment. As the sponsor failed to establish the equivalence of the compared products in terms of efficacy, the claim of major contribution to patient care could not be accepted.

In the context of the initial review, a negative opinion was adopted by the COMP. The sponsor's appeal comprises two grounds. Under the first ground of appeal, and in support of a claim of clinically relevant advantage, the sponsor focuses on alleged limitations in the availability of CAR-T cell therapies resulting in alleged harm for r/r DLBCL patients (Ground 1). Under the second ground of appeal, the sponsor claims that Zynlonta provides supposedly a clinically relevant advantage for specific subsets of r/r DLBCL patients (Ground 2). The specific arguments in support of Grounds 1 and 2 are partly overlapping and are discussed below.

These grounds for maintaining the orphan designation are different from the arguments submitted in the initial maintenance report and discussed during the oral explanation in October 2022 in that the sponsor is not claiming significant benefit due to a more favourable safety profile, better efficacy in leukapheresed population, or major contribution to patient care over the authorised satisfactory methods of treatment.

However, before discussing the detailed arguments from the sponsor, it bears recalling that the COMP requires conclusive evidence in support of any significant benefit claims made. It is also important to bear in mind that the efficacy of Zynlonta has shown to be inferior compared to the authorised CAR-T cell products Yescarta and Breyanzi; and that Zynlonta had numerically lower Complete Remission Rates (CRR) as compared to Kymriah.

<u>Ground 1: Significant benefit because of the serious limitations on availability of CAR-T cell therapy resulting in harm for r/r DLBCL patients</u>

First, the sponsor presents data in support of the claim that there are serious limitations on the availability of CAR-T cell therapies throughout the EU (4.2). Second, the sponsor presents data in support of their claim of patient harm as a result of the CAR-T cell therapy availability limitations (4.3). Third, the sponsor presents data in support of the claim that Zynlonta can address the limitations on availability of CAR-T cell therapy for r/r DLBCL patients (4.4).

As noted in the appeal, the sponsor "*fully realises that lack of availability of existing therapies only exceptionally supports a finding of significant benefit*" (emphasis added).

Indeed, the 2016 "Commission notice on the application of Articles 3, 5 and 7 of Regulation (EC) No 141/2000 on orphan medicinal products" (2016/C 424/03; "2016 Commission Notice", hereinafter) clarifies that "*significant benefit should not be based on possible increased supply/availability due to shortages of existing authorised products or to existing products being authorised in only one or a limited number of Member States (exceptions may be made if the sponsor has evidence of patient* harm" (emphasis added).

In this respect, it also bears recalling briefly the framework for the authorisation of a medicinal product as orphan on the basis of a finding of significant benefit vis-à-vis (already authorised) satisfactory methods of treatment. In accordance with the established case-law of the Court of Justice of the European Union, "it is apparent from the wording of Article 3(1)(b) of Regulation No 141/2000 and the spirit underlying the system established by that regulation that the criteria for a finding of significant benefit are strict" (emphasis added; in this respect, see: judgment of the General Court of 5 December 2018 in BMS v Commission and EMA, T-329/16, EU:T:2018:878, paragraph 101).

Further, it should be noted that, in the absence of conclusive evidence proving significant benefit at the time of the marketing authorisation, the COMP is required to conclude that the designation criteria laid down in Article 3 of Regulation (EC) No 141/2000 are no longer met and, therefore, recommend that the Commission should remove the medicinal product concerned from the Community Register of orphan medicinal products (in this respect, see: judgment of the General Court of 5 December 2018 in *BMS v Commission and EMA*, T-329/16, EU:T:2018:878, paragraph 86). This requirement is aligned with the fact that, for the purpose of maintenance of orphan designation, the comparative analysis between the new medicinal product and the reference product must establish not only that the new product provides a benefit to patients but also that benefit is significant (in this respect, see: judgment of the General Court of 16 May 2019 in *GMPO v Commission*, T-733/17, EU: T:2019:334, paragraph 39).

According to the SmPC (section 4.2) of the currently authorised CAR-T cell products, all have to be given in qualified treatment centres, whereas Zynlonta must only be administered under the supervision of a healthcare professional experienced in the diagnosis and treatment of cancer patients. Under this section of the appeal, the sponsor points out that several member states have limited (one centre Bulgaria, Croatia, Denmark, Ireland, Norway, Romania, Slovenia, Slovakia) or none (Cyprus, Latvia, Lithuania, Luxembourg, Malta, Estonia) CAR-T cell treatment centres. In addition, the sponsor notes that patients have to be in the vicinity of the specialised centre until at least 4 weeks after treatment for safety monitoring.

While the COMP acknowledged these arguments, no data was presented which would suggest that patients in these countries with few/no qualified CAR-T cell treatment centres are not adequately managed resulting in patient harm.

In particular, as acknowledged by the sponsor, the Union legal framework (in particular, Regulation (EC) No 883/2004 of the European Parliament and of the Council of 29 April 2004 on the coordination

of social security systems and Directive 2011/24/EU of the European Parliament and of the Council of 9 March 2011 on the application of patients' rights in cross-border healthcare) facilitates the treatment of patients in other Member States. As noted in the 12 May 2022 "Report from the Commission to the European Parliament and the Council on the operation of Directive 2011/24/EU on the application of patients' rights in cross-border healthcare" (COM(2022) 210 final), "*[t]he Directive has had a substantial impact in the area of rare diseases with the creation of the ERNs to support the diagnosis and treatment of rare disease patients*" (emphasis added).

The fact that, generally speaking, "*cumbersome and disproportionate administrative procedures [that] undermine citizens' rights to cross-border healthcare* [exist] *in some Member States*" does not entail that patients in the EU do not have, in particular, access to CAR-T cell treatment.

On balance, the fact that there are limited qualified treatment centres in some Member States does not demonstrate the lack of availability of CAR-T cell treatment in the EU; let alone any patient harm as a result of such alleged lack of availability.

Last, and without prejudice to the above, the COMP noted that it is currently not known what the future availability of Zynlonta will be across the EU. The sponsor did not provide any evidence to that effect.

(4.2.2) The sponsor also discusses possible availability constraints of CAR-T cell products at individual patient level, owing to specific manufacturing challenges of these products combined with rapid disease progression. Across the 3 autologous CAR-T cell therapies investigated in large clinical studies, patients had to wait a median time between 2 weeks and more than 50 days, but organizational and process-related problems can further prolong the time from leukapheresis to CAR-T cell product delivery (vein to vein time) or, in some cases, the manufacturing may even fail. In these situations, an "off-the-shelf" medicinal product for immediate administration, such as Zynlonta, may be an alternative treatment option, especially when the disease progresses rapidly.

While the manufacturing challenges at individual patient level are acknowledged by the COMP, it is pointed out that failed initial manufacturing attempts may be successful in a subsequent manufacturing attempt for an individual patient. The fact that the initial manufacturing of CAR-T cell products may not end up being successful for some patients (whose identity, incidentally, is not possible to ascertain a priori, before the manufacturing attempt) does not entail that CAR-T cell therapy will not be eventually available for those patients; or that those patients are exposed to patient harm. It is noted that CAR-T-cell products were more effective than Zynlonta in indirect comparisons, also when patients for whom the production of CAR-T cells was not successful and thus could not be administered during the pivotal studies were taken into account.

Furthermore, the link between CAR-T cell manufacturing challenges at individual patient level and a recognized "shortage" in overall CAR-T cell availability was not considered established by the data presented.

Last, and without prejudice to the above, the COMP also notes that none of the authorised CAR-T cell products is mentioned in the EMA's published catalogue of shortages: https://www.ema.europa.eu/en/human-regulatory/post-authorisation/availability-medicines/shortages-catalogue

With regard to the duration of the CAR-T cell product manufacturing in relation to the dynamics of disease progression, the COMP considers that this is overlapping with the arguments on Ground 2 below, more specifically (5.2) of the sponsors arguments, and will be discussed below.

(4.2.3) The sponsor also summarizes reports on actual use of CAR-T cell therapies in several EU member states. Based on a survey conducted in Germany, France, Italy, Spain, and the United Kingdom in 2022, among patients treated with systemic therapy alone in a third-line setting of r/r DLBCL, only 26% received CAR-T cell therapies (13% each, for Yescarta and Kymriah) (CancerMPact® 2022). An analysis conducted to examine patient access to CAR-T cell therapies in Italy using publicly available data and to uncover potential systemic barriers indicated that in 2020 around 190 Italian DLBCL patients were not treated with a licensed CAR T-cell therapy despite being CAR-T eligible under the criteria defined by AIFA (Jommi et al. 2022). The reasons for this were mainly linked to the complexity of these resource-intense therapies including structural and organizational challenges (specialized treatment centers, product manufacturing, etc).

These arguments were duly noted by the COMP, but similar to the above, no data was presented which would link the sponsor's observations to patient harm in the respective EU member states. The fact that that 26% of patients in the third-line setting of r/r DLBCL received CAR-T cell therapies does not entail that the remaining patients did not have access to CAR-T cell treatment or that they were exposed to patient harm. In principle, the recommendation of the treatment of patients in any setting (and, in particular, at an advanced stage of DLBCL) rests with the treating physicians, who may at their discretion recommend an alternative course of disease management. Further, the treatment strategy is discussed, as applicable, between the treating physicians and the respective patient. The fact that CAR-T cell treatment was not followed for the remaining patient population in this setting does not necessarily mean that such treatment was not available; or that patients were otherwise exposed to harm.

As regards the access data for DLBCL CAR T-cell therapy by Jommi et al. (2022), the COMP pointed out that this analysis is based on data from 2020 and is not representative of the current situation in Italy, where 30 CAR-T cell treatment centers exist. Moreover, new treatment options have obtained marketing authorisation recently, such as the CAR-T cell therapy Breyanzi.

(4.3) The sponsor further summarized available data to support the argument of patient harm resulting from (timely) CAR-T cell therapy availability limitations. The sponsor mentions that in the pivotal licensing studies for Yescarta, Kymriah and Breyanzi between 9% to 30% of enrolled patients could not receive the final CAR-T cell product mainly due to disease progression and death of patients or because of manufacturing failure.

The COMP pointed out that for Yescarta and Breyanzi the efficacy results from the MAIC analysis versus Zynlonta, in the ITT (FAS for Yescarta) populations (including all leukapheresed patients, independent of receiving the final CAR-T cell product or not), still statistically favoured the CAR-T cell products over Zynlonta. This was already discussed during the initial review procedure, leading to the negative outcome and is reflected above in this report.

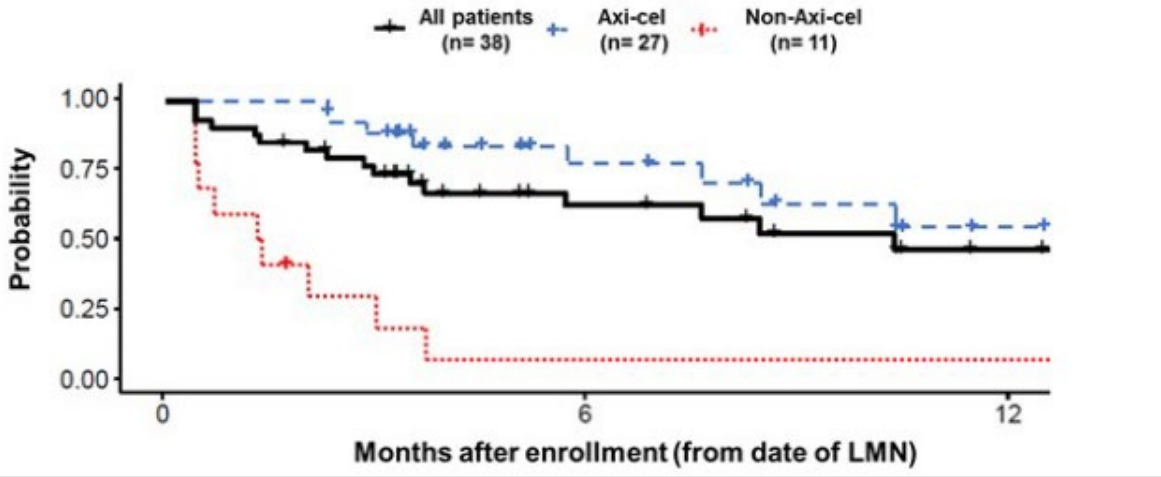
Similar analyses of r/r DLBCL patients intended to receive CAR-T cell therapy and who underwent the initial step of leukapheresis but could not receive the final product due to disease progression are presented by the sponsor (Kwon et al. 2022; Bachy et al. 2022; Chiappella et al. 2021). In more detail, an analysis by Mian et al (2019) is described. The authors compared in an ITT analysis OS of r/r DLBCL patients who received Yescarta and patients for whom Yescarta therapy was intended but not administered (Figure 2). A total of 27 patients (71%) received Yescarta and 11 patients (29%) were considered candidates but could not receive Yescarta (7 patients died prior to leukapheresis, 3 patients died after leukapheresis but prior to CAR-T cell infusion). The results from this analysis showed that patients who could not receive Yescarta had a higher comorbidity index at the time of decision to proceed with CAR-T cell therapy; the majority of them died before leukapheresis from disease

progression or complications of prior treatment. Outcomes were analysed and showed that the median OS in the non-infused patients was much shorter than in the Yescarta-infused groups (1 month [95% CI: 0.4 to 3.7] and 13 months [95% CI: 7.7 to N.R]), (Figure 2).

While the COMP acknowledged these data, it emphasized that the impact of Zynlonta on the efficacy outcome of these patients who could not receive/benefit from the authorised CAR-T cell products (e.g. due to rapid disease progression) is not clear and no conclusive efficacy data in this specific population is available. In the analysis described by Mian et al (2019), the authors state that patients who could not receive Yescarta had a higher comorbidity index at the time of decision to proceed with CAR-T cell therapy. Furthermore, the median number of prior therapies was 4 in these patients, as compared to 3 in those patients who did receive CAR-T cell therapy.

The COMP also noted that, in the article by Mian et al (2019), the authors call for improved strategies to bridge patients with aggressive B-cell lymphoma intended to receive Yescarta until they can be administered the final CAR-T cell product. The sponsor themselves did not suggest Zynlonta as a bridging therapy and the CHMP noted in their assessment report that this requires further exploration.

Figure 2. Overall Survival by CAR-T cell (Yescarta/axi-cel) Status



Axi-cel: axicabtagene ciloleucel ; CAR-T: Chimeric antigenic receptor-T ; ITT: Intent-to-treat; LMN : Letter of medical necessity; Tisa-cel: tisagenlecleucel.
Overall survival of all patients (solid line) intended to receive Axi-cel and patients who ultimate did (dashed line) or did not (dotted line) receive Axi-cel. Analysis is performed on intent to treat (ITT) from date of letter of medical necessity (LMN) seeking approval for CAR-T cell therapy. Source: Mian et al, 2019

(4.4) The last line of argumentation in the context of Ground 1 relates to evidence on how Zynlonta can address the supposed limitations on availability of CAR-T therapy for r/r DLBCL patients. In this regard the sponsor mentions 1) the expected "easy access" to Zynlonta for all patients with r/r DLBCL since the administration does not require qualified treatment centres and 2) "immediate availability" associated with a rapid time to response (median time to first response of 41 days).

The COMP noted that this line of argumentation is premised on the claim that CAR-T cell therapies have "*serious limitations on availability*". As explained above, the COMP does not accept that CAR-T cell therapies are unavailable in the EU, let alone to such extent that their unavailability results in patient harm. The fact that CAR-T cell treatments are administered at qualified treatment centers does not entail that they are unavailable. Similarly, the fact that a new medicinal product may be more readily available does not mean that the previously authorised products are not available. Furthermore, the COMP emphasized again that the fact that CAR-T cell treatment may not be followed

at individual patient level (e.g. on the basis of the treatment strategy discussed between the treating physicians and the patient) does also not entail that these products are unavailable. At present, there is no consensus among learned societies and physicians regarding exclusion criteria for CAR-T cell therapy, further to the authorised therapeutic indication (SmPC). Therefore, the final treatment choice remains at the discretion of the individual treating physician.

Without prejudice to the above, the COMP took note of the sponsor's claims as to the availability of Zynlonta, but also pointed out that at present no information on the expected availability/access of/to Zynlonta throughout the EU is available. The sponsor has not submitted any information to the COMP showing that Zynlonta will be readily available in the EU (let alone in all Member States).

Ground 2: Zynlonta provides a clinically relevant advantage for specific subsets of r/r DLBCL patients
The sponsor proposes that compared to CAR-T cell treatment, their product provides a significant benefit for at least three specific subsets of r/r DLBCL patients, namely those who: (5.1) were unsuccessfully treated with CAR-T cell therapy; (5.2) cannot be treated in time with CAR-T cell therapy because of rapid disease progression and the time needed to prepare a CAR-T cell product; (5.3) are deemed ineligible for CAR-T cell therapy.

(5.1) R/R DLBCL patients unsuccessfully treated with CAR-T cell therapy: the arguments and data presented by the sponsor on this point were already discussed during the initial review of the orphan designation criteria. No new arguments/data are presented by the sponsor. The COMP previously concluded that "*The data on individual patients failing prior treatment with CAR-T cell therapy before study entry were considered inconclusive in view of the overall low number of patients in this subset, limited information on the type of treatment received and with limited follow-up, so that the clinical relevance of responses could not be reliably determined*", please see above.

(5.2) Patients who, because of rapid disease progression, cannot receive CAR-T cell treatment in time: the sponsor has referred to this aspect also under the first ground for appeal (4.2.2). In particular, the sponsor considers that Zynlonta will address an unmet medical need in patients with rapid disease progression as it is an "off-the-shelf" medicinal product for immediate administration. The COMP acknowledged these arguments but noted that 1) there are no specific criteria at present which would allow to pre-define a specific patient population not benefiting from CAR-T cell therapy but benefitting from Zynlonta instead and 2) that choice of treatment is at the individual discretion of the treating physician and 3) the efficacy of Zynlonta in patients with rapid disease progression and who cannot receive CAR-T cell therapy in time has not been demonstrated. These patients may have a more aggressive disease course and/or possible other adverse prognostic characteristics, as described for example by the OS analysis conducted by Mian et al. (2019) and which is described above under (4.3), Figure 2. In this retrospective ITT analysis, approximately one third of patients with r/r aggressive B-cell lymphoma for whom CAR-T cell therapy was intended were unable to receive it and had extremely short median OS. Patients who could not receive Yescarta had a higher comorbidity index at the time of decision to proceed with CAR-T cell therapy. It would therefore be important to have efficacy data with Zynlonta in this specific patient cohort in order to support the claim of a clinically relevant advantage for this specific subset of r/r DLBCL patients. However, no such data has been presented by the sponsor. With regard to the possibility of using Zynlonta as a bridging therapy to help control disease in patients who are rapidly progressing (while awaiting CAR-T cell therapy), the CHMP concluded in their report that "*Although Zynlonta may facilitate bridging to CAR-T treatment, the efficacy of this treatment after Zynlonta needs further exploration" (*please see for more details above, under (4.3)). A claim for clinically relevant advantage of Zynlonta as bridging therapeutic in patients with rapid disease progression can therefore also not be supported by the COMP, due to lack of conclusive data.

The sponsor makes reference to the Zynlonta CHMP Assessment Report (AR) on several occasions in their orphan maintenance appeal report. These passages are derived from the part of the CHMP AR that discusses the granting of a conditional marketing authorisation, in the absence of comprehensive data on the product:

1) Zynlonta "… *with its new mechanism of action (in the treatment of DLBCL) as well as its immediate availability, is considered to fulfil this unmet medical need".*

2) *"CAR-T therapies are only available at specialized centres and up to 30% of eligible patients may not be able to receive the planned therapy, either due to manufacturing problems or rapid disease progression".*

With regard to points 1) and 2), the COMP pointed out that "[…] *applicants should bear in mind that provisions on conditional marketing authorisations differ in their nature from provisions on data to support orphan medicinal products. Orphan medicinal products benefit from market exclusivity, the protection of which requires a strict interpretation. Recommending a conditional marketing authorisation by the CHMP does not imply a confirmation of significant benefit (to be assessed by the COMP)*". In that respect, reference is made to the "Guideline on the scientific application and the practical arrangements necessary to implement Commission Regulation (EC) No 507/2006 on the conditional marketing authorisation for medicinal products for human use falling within the scope of Regulation (EC) No 726/2004" (EMA/CHMP/509951/2006, Rev.1).

The COMP has explained above the reasons for which possible manufacturing problems or rapid disease progress do not establish the existence of serious availability limitations and of patient harm (as claimed by the sponsor). Without prejudice to the above, the CHMP Assessment Report (on the distinct matter of the requirement of fulfilling an unmet medical need, which must be met specifically for the granting of a conditional marketing authorisation; namely, an authorisation based on less comprehensive clinical data) does not take a position on any supposed patient harm (within the meaning of the 2016 Commission Notice) as a result of the availability/unavailability of CAR-T cell therapies in the EU.

In addition, with regard to point 1), the COMP pointed out that according to the 2016 Commission Notice (2016/C 424/03), "'*Significant benefit' should not be based on* […] *an alternative mechanism of action* per se*. However, in exceptional cases consideration may be given to those developments at the time the designation is granted. At the time the criteria are reviewed for the purposes of granting the marketing authorisation, this must translate into a clinically relevant advantage or a major contribution to patient care*". In other words, the simple availability of a medicinal product with a new mechanism of action does not result in a finding of significant benefit, unless accompanied by (conclusive) data demonstrating the existence of a clinically relevant advantage or a major contribution to patient care.

The COMP emphasized again that conclusive evidence is expected in support of claims made in relation to significant benefit. The COMP considers that based on the data presented (both in isolation and in their totality), a positive conclusion cannot be made on a clinically relevant advantage of Zynlonta vis-à-vis the authorised satisfactory methods (Yescarta, Kymriah, and Breyanzi).* MAIC between the patient populations from the pivotal clinical trials showed a statistically significant inferior efficacy of Zynlonta in comparison to Yescarta and Breyanzi. Even when including all leukapheresed patients in these indirect efficacy analysis (also those not receiving the final CAR-T cell products due to disease progression, death or manufacturing failure), i.e. the so called "intention-to-treat" (ITT) population (or full analysis set for Yescarta), the efficacy results still statistically favoured Yescarta and Breyanzi over Zynlonta.

** For completeness, the sponsor abandoned at the stage of the appeal the claim of major contribution to patient care (which had been separately refused by the COMP in the context of the initial Opinion; see above).*

(5.3) Patients deemed ineligible for CAR-T cell treatment based on the benefit-risk- assessment: the sponsor notes that it is critical to identify patients who are likely to benefit from CAR-T cell therapy, taking into account the possible toxicities (Kittai et al. 2020; Di Rocco et al. 2020) in order to determine the patients that would derive maximum benefit from CAR-T cell therapy and the patients for whom the possible toxicities would outweigh the potential benefits. In the absence of appropriate published guidelines and of a clear consensus among physicians regarding appropriate selection criteria for CAR-T cell products, each country/institution has its own definition of eligibility for CAR-T cell products mainly based on patient's age, performance status and concomitant comorbidities. Section 4.4 of the SmPCs of the CAR-T cell therapies provide general guidance for patient selection that may be considered eligible for this treatment, although these are not strict contra-indications. In brief, the approved SmPCs indicate that patients considered for CAR-T cell therapy should have r/r disease that is not rapidly progressing to allow time for leukapheresis, manufacturing, and infusion of the CAR-T cells. Patients should not have an active, uncontrolled infection, or a diagnosis of primary CNS lymphoma. Finally, it is recommended that patients have adequate renal, hepatic, pulmonary, and cardiac function (although the exact parameters vary slightly between products). Furthermore, observational studies indicated that severe Cytokine Release Syndrome (CRS) was significantly associated with a poor Eastern Cooperative Oncology Group performance status (PS 2-4) and high age (>65y).

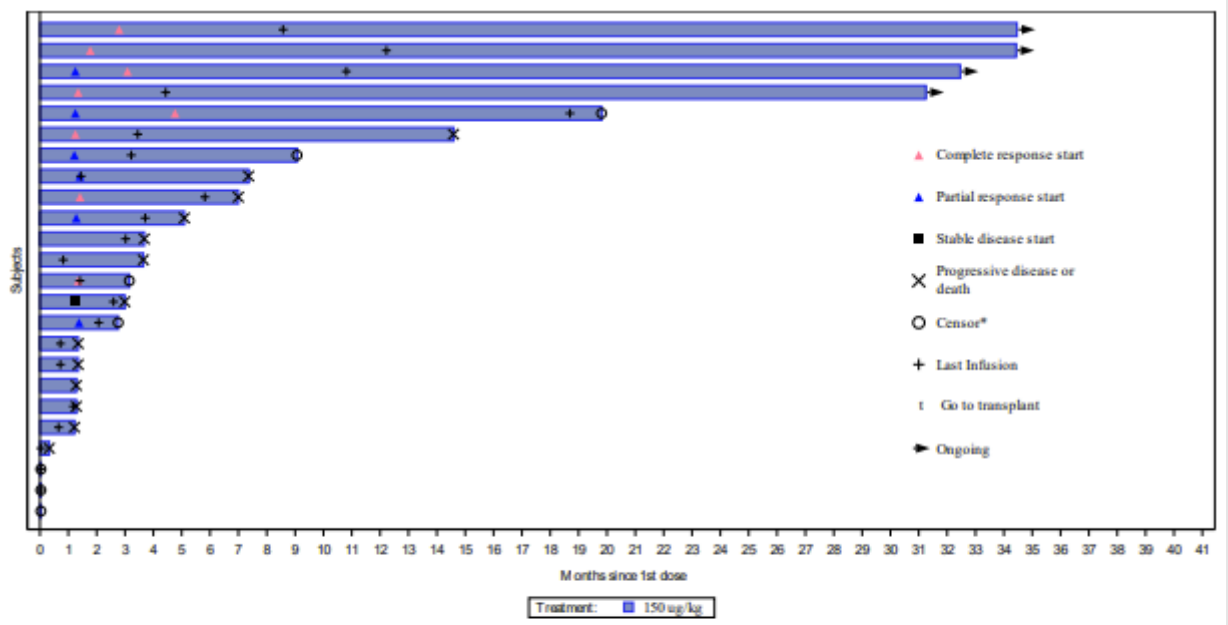
While the COMP acknowledged the sponsor's arguments, it emphasized that the study population of the pivotal licensing study of Zynlonta is not considered to constitute a patient population who would be ineligible for CAR-T cell therapy per se. There are no strict contra-indications for the use of CAR-T cell products in the respective SmPCs; but based on clinical judgement and guidance in the SmPC, very frail patients, patients with rapid progressive disease, primary CNS lymphoma, active graft versus host disease, uncontrolled infection and patients not recovered from serious adverse reactions from preceding chemotherapies may not be considered eligible or should be treated with care. However, the COMP did not consider that the overall study populations from the main clinical trials with Zynlonta represent a frail patient population per se, who may not be considered a candidate for CAR-T cell treatment as described in the SmPC of those products. E.g. by protocol, patients with *significant cardiovacular or comorbidities, poorly controlled diabetes, severe chronic pulmonary disease, were excluded from the Zynlonta studies. Also patients with lymphoma with active CNS involvement and graft vs host disease were excluded. Neither were patients not recovered from acute adverse events of previous therapy eligible (with the exception of alopecia and mild lower neuropathy).* Also, in the SmPC of Zynlonta, warnings are included not to treat patients with severe infections (grade 3-4), given that neutropenia is a common adverse event of this product.

In the main study of Zynlonta (Study 201, an uncontrolled study in 145 DLBCL patients, the selected patients had in general a good or reasonable performance state (93.8% ECOG 0-1). The main reason for exclusion during screening (thus before the start of the study) was lack of adequate organ function (16/37) followed by ECOG score above 2 (5/37), and bulky disease ≥10 cm (3/37). This further illustrates that the Zynlonta studied population is a patient population that is not considered to be ineligible for CAR-T cell therapy per se.

(5.3.1) Pivotal Study ADCT-402-201 (LOTIS-2) Subgroup Analysis of r/r DLBCL Patients in whom the risks of CAR-T cell toxicities would outweigh the potential treatment benefit: the sponsor performed a post-hoc analyses in a subgroup of patients from the pivotal phase 2 study LOTIS-2 that met one of

the following criteria: ≥75 years of age OR with ECOG PS=2. Furthermore, none of these patients received prior or subsequent CAR-T cell therapy. The sponsor considers that because of the reasons of advanced age and/or poor performance status, the risks of CAR-T cell toxicities would outweigh the potential treatment benefits in these patients. A total of 24 patients were included. There were 19 patients (79.2% of the subgroup) ≥75 years of age, with 2 patients ≥85 years of age. A total of 9 patients (37.5%) had an ECOG score of 2. All 24 patients had received prior systemic anticancer therapy with a median number of prior lines of 3 (ranging from 2 to 5). The sponsor reports that Zynlonta showed a "substantial and remarkable" response in this subgroup of patients with an ORR of 50.0% and CRR of 33.3%. The efficacy was sustained with a median DOR not reached after 28 months. The median PFS was 5.09 months, and the median OS was 7.36 months (Figure 3).

Figure 3. Swimmer Plot in the Post-hoc Subgroup (All-Treated Population)[a] (as per Annex 1 of sponsor's documents)



CAR-T=Chimeric Antigenic Receptor-T; ECOG= Eastern Cooperative Oncology Group.
(a) Subset of patients with baseline ECOG=2 or age ≥75 years of age who did not receive prior or subsequent CAR-T therapy.
Each bar represents one patient in the study. Response is determined by independent reviewer.
* Only for censored patients who discontinued trial due to reasons other than progression or who went onto a different anticancer treatment other than transplant.

While the results from this sub-analysis are acknowledged by the COMP, it is noted that the general study population where this selected subgroup stems from, is not representative of a frail population with rapidly progressive disease, given the inclusion and exclusion criteria (please refer to the above point (5.3)).

The COMP also noted that this sub-group was small and not pre-specified in the study protocol which hampers drawing final conclusions on the efficacy of Zynlonta in this patient group.

To be noted, the studies with the CAR-T cell product Breyanzi also included a number of very elderly patients ≥ 75 years (27) and nine patients with ECOG PS 2, with r/r DLBCL. No pooled analysis of these subsets is available, but the ORR in the very elderly was 20/27 (74%), median DOR was not reached). Out of the 9 patients with ECOG PS 2, five achieved a CR (DOR range 0.7-5.3 months, OS 127-653 days, corresponding with approximately 4-27 months) (source EPAR Breyanzi). Like in the

pivotal study with Zynlonta, the numbers of these specific patients were limited, and it is difficult to draw final conclusions on efficacy for either product. However, the response does not appear less favourable for Breyanzi, as compared to Zynlonta.

In conclusion (relating to Ground 2), the COMP considers that there is a lack of conclusive evidence to support the efficacy of Zynlonta in specific patient subsets which, according to the sponsor, are 1) unlikely/cannot benefit from the authorised CAR-T cell products Yescarta, Kymriah and Breyanzi or 2) have progressed following previous treatment with authorised CAR-T cell products.

In conclusion (relating to Ground 1 and 2), the COMP does not consider the arguments and data presented by the sponsor as conclusive evidence in support of the sponsor's appeal grounds, to establish a significant benefit of Zynlonta vis-a vis the authorised CAR-T cell products Yescarta, Kymriah and Breyanzi.

In relation to the first ground of appeal, the COMP considers that the presented data is not sufficient to establish the lack of availability of the authorised CAR-T cell products Yescarta, Kymriah and Breyanzi in r/r DLBCL patients, or the existence of patient harm for these patients as a result of this claimed lack of availability.

In relation to the first and second grounds of appeal, the COMP considers that the presented data is not sufficiently robust to conclude that Zynlonta provides a clinically relevant advantage for specific subsets of r/r DLBCL patients vis-à-vis the authorised CAR-T cell products Yescarta, Kymriah and Breyanzi.

7. COMP final position on review of criteria for orphan designation adopted on 10 November 2022

Based on the assessment of the detailed grounds for appeal and the argumentations presented by the sponsor during the oral explanation, 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;
- in the context of the first opinion, the COMP concluded that the data submitted by the sponsor did not allow a positive conclusion on the claim for significant benefit of loncastuximab tesirine over the satisfactory methods of treatment for adult patients with relapsed or refractory DLBCL and HGBL in the third- and later lines setting. The COMP considered that the sponsor's claim that Zynlonta is of significant benefit to those affected by the orphan condition does not hold since the sponsor could not establish the existence of a clinically relevant advantage over Yescarta, Kymriah and Breyanzi which are authorised satisfactory methods of treatment.
  - A different safety profile of Zynlonta compared to the approved CAR-T cell products cannot be concluded as being better based on the limited experience with Zynlonta and in the setting of an indirect comparison where confounding by indication and selection bias cannot be excluded.
  - In addition, matching-adjusted indirect comparisons between the patient populations from the pivotal trials for Zynlonta and the approved CAR-T cell products, which were considered as satisfactory methods of treatment for the target patient population, showed a statistically significant inferior efficacy of Zynlonta in comparison to Yescarta and Breyanzi.
  - The data on individual patients failing prior treatment with CAR-T cell therapy before study entry were considered inconclusive in view of the overall low number of patients in this subset, limited information on the type of treatment received and with limited follow-up, so that the clinical relevance of responses could not be reliably determined.
  - Furthermore, the claim for major contribution to patient care cannot be accepted when the efficacy is not established as being comparative.
- In the context of the appeal, the sponsor presented evidence and arguments to the COMP to substantiate the claim of a clinically relevant advantage of Zynlonta in comparison to authorised CAR-T cell products. The appeal comprises two grounds. Under the first ground of appeal, the sponsor claims that there are limitations on the availability of the authorised CAR-T cell products resulting in patient harm; and those alleged serious limitations will be overcome through the better availability of Zynlonta. Under the second ground of appeal, the sponsor claims that Zynlonta, when compared to CAR-T cell treatment, provides a clinically relevant advantage in specific subsets of relapsed or refractory DLBCL patients;

  - In relation to the first ground of appeal, the COMP considers that the presented data is not sufficient to establish the lack of availability of the authorised CAR-T cell products Yescarta, Kymriah and Breyanzi in relapsed or refractory DLBCL patients, or the existence of patient harm for these patients as a result of this claimed lack of availability.
  - In relation to the first and second ground of appeal, the COMP considers that the presented data is not sufficiently robust to conclude that Zynlonta provides a clinically relevant advantage for specific subsets of relapsed or refractory DLBCL patients vis-à-vis the authorised CAR-T cell products Yescarta, Kymriah and Breyanzi.
- therefore, the sponsor has not established that Zynlonta is of significant benefit to those affected by the condition.

The COMP, having considered the detailed grounds for appeal submitted by the sponsor and all the supporting data 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 not satisfied.

The COMP recommends that Zynlonta, loncastuximab tesirine for treatment of diffuse large B-cell lymphoma (EU/3/21/2481) is removed from the Community Register of Orphan Medicinal Products.