24 May 2022
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Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Polivy (Polatuzumab vedotin)
Treatment of diffuse large B-cell lymphoma
EU/3/18/2013

Sponsor: Roche Registration GmbH

Note

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

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1. Product and administrative information

Product	
Designated active substance	Polatuzumab vedotin
Other name	Polivy
International Non-Proprietary Name	Polatuzumab vedotin
Tradename	Polivy
orphan condition	Treatment of diffuse large B-cell lymphoma
Sponsor's details:	Roche Registration GmbH Emil-Barell-Strasse 1 Grenzach 79639 Grenzach-Wyhlen Baden-Wuerttemberg Germany
Orphan medicinal product designation procedural history	
Sponsor/applicant	Roche Registration Limited
COMP opinion	15 March 2018
EC decision	16 April 2018
EC registration number	EU/3/18/2013
Post-designation procedural history	
Transfer of sponsorship	Transfer from Roche Registration Limited to Roche Registration GmbH. – EC decision of 25 July 2018
Type II variation procedural history	
Rapporteur / Co-rapporteur	Alexandre Moreau / Jan Mueller-Berghaus
Applicant	Roche Registration GmbH
Application submission	05 November 2021
Procedure start	27 November 2021
Procedure number	EMA/H/C/004870/II/0012
Invented name	Polivy
Proposed therapeutic indication	Polivy in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone (R-CHP) is indicated for the treatment of adult patients with previously untreated diffuse large B-cell lymphoma (DLBCL). Further information on Polivy can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/Polivy
CHMP opinion	24 March 2022
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Karri Penttila / Maria Elisabeth Kalland
Sponsor's report submission	03 December 2021
COMP discussion	15-17 March 2022
COMP opinion (adoption via written procedure)	25 March 2022

2. Grounds for the COMP opinion

The COMP opinion that was the basis for the initial orphan medicinal product in 2017 designation was based on the following grounds:

- the intention to treat the condition with the medicinal product containing polatuzumab vedotin was considered justified based on clinical observations supporting improved survival in relapsed/refractory patients when the proposed treatment is added on to other existing treatments;
- the condition is chronically debilitating due to involvement of single or multiple nodal or extra nodal sites, including the gastrointestinal tract and bone marrow and life-threatening with 5-year survival rates reported as low as approximately 25% for high risk patients;
- 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.
- 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 polatuzumab vedotin will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical and preliminarily clinical observations in relapsed/refractory patients supporting add-on effects in terms of clinical response and survival, when the product is combined with other existing treatments. The Committee considered that this constitutes a clinically relevant advantage.

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

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

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

Condition

Diffuse large B-cell lymphoma (DLBCL) is the most common histological subtype of non-Hodgkin's lymphoma (NHL) in adults. It comprises a group of aggressive lymphoid malignancies histologically characterised by dense proliferation of neoplastic B-cells.

DLBCL arises from a mature B-cell and is usually comprised of cells resembling large centroblasts or immunoblasts, two distinct types of activated B-cells. These cells typically express the B-cell markers CD19 and CD20 as well as other surface markers characteristic for B-cell lineage (Martelli et al., 2013). The molecular pathogenesis of DLBCL is complex and includes both genetic lesions that are relatively specific for this disease (i.e., rearrangements of BCL6) and molecular alterations that are shared with other NHL variants. In addition to occurring de novo, DLBCL can arise through the transformation of many different types of low-grade B-cell lymphomas, including B-cell chronic lymphocytic leukaemia (e.g., Richter's transformation), lymphoplasmacytic lymphoma, follicular lymphoma, marginal zone (MALT) lymphoma, and splenic marginal zone lymphoma.

Patients with DLBCL often present with single or multiple rapidly enlarging symptomatic masses, with up to 40% occurring at extra-nodal sites (Martelli et al., 2013). The disease usually affects adults, especially around the age of 60 to 70 years, but also rarely occurs in adolescents and children.

In 2016, the WHO updated the previous 2008 classification of lymphoid neoplasms to include 2 sub-types 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 'high grade B-cell lymphoma with MYC, BCL2 and/ or BCL6 translocations' (HGBL-DH and HGBL-TH) was created for all double- or triple hit lymphomas (DHL/THL) other than follicular lymphomas or lymphoblastic lymphomas. Overall, HGBL-DH/TH represented about 8% of cases of DLBCL (Scott et al., 2018). Despite these changes in sub-classifications, the condition DLBCL is still considered a suitable orphan condition.

The approved therapeutic indication "*Polivy in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone (R-CHP) is indicated for the treatment of adult patients with previously untreated diffuse large B-cell lymphoma (DLBCL)*" 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 (B/R) 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, local symptoms of lymphadenopathy, end-organ damage from disease involvement, and bone marrow failure that may lead to infections, anaemia, and thrombocytopenia.

The sponsor also discussed the life-threatening nature of the disease with a median survival of less than one year if left untreated. The International Prognostic Index (IPI) for aggressive NHL identifies five factors obtained at diagnosis that are prognostic for outcomes including progression-free survival (PFS) and overall survival (OS). Patients with higher IPI scores, combined with biologically defined higher-risk patients (including the ABC, DHL, and DEL subtypes of DLBCL), represent the subset of patients with the poorest outcomes with current therapies. For example, patients with IPI 3-5 have a 5-year PFS ranging from 39% to 54% (Zhou et al., 2014). Furthermore, of the patients who proceed to transplant, only 30 to 40% will be cured (Gisselbrecht et al., 2010; Crump et al., 2017). However, most patients with relapsed or refractory (r/r) DLBCL are ineligible for autologous stem cell transplantation (ASCT) due to their age, co-morbidities or chemotherapy insensitive disease and the treatment approach for such patients in the second line setting as well as for all patients beyond second line is a palliative approach. New therapies and regimens represent considerable progress in r/r DLBCL, but the outcome of patients treated in each subsequent lines of therapy is progressively poorer, and most patients either do not respond or do not have a durable response to these treatments (Sehn et al., 2021).

The COMP agreed that the condition remains chronically debilitating due to constitutional symptoms, local symptoms of lymphadenopathy, end-organ damage from disease involvement, and bone marrow failure that may lead to infections, anaemia, and thrombocytopenia, and life-threatening in patients with r/r disease who do not respond to treatment.

Number of people affected or at risk

The sponsor performed a review of epidemiological data to establish the prevalence of DLBCL in Europe. Published data on prevalence for DLBCL were directly extracted from the population-based cancer registries for the Nordic countries (NORDCAN: Denmark, Faroe Islands, Finland, Greenland, Iceland, Norway, and Sweden; 2019 data), the Integraal Kankercentrum Nederland (IKNL, The Netherlands; 2021 data), the Italian Association of Cancer Registries (AIRTUM, Italy; 2020 data), the national Slovenian Cancer Registry (2018 data), the German cancer registry Robert Koch Institute (2018 data), the Spanish Registry (REDECAN; 2020 data), and the Belgium Cancer Registry (2018 data). Prevalence data for non-EU countries were also obtained from the two population-based cancer registries the Haematological Malignancy Research Network (HMRN: Yorkshire region in the UK; 2004-2016 data), and the Surveilance, Epidemiology, and End Results (SEER) program in US (representing 28% of the US population; 2018 data) as points of reference. The prevalence estimates (per 10,000) extracted from these databases with cancer statistics in the 27 EU countries (EU27), UK and USA are presented in Table 1.

The sponsor argued that not all patients who have ever been diagnosed with DLBCL and are alive today should be considered a "DLBCL patient" because firstly, after approximately 2 years post diagnosis, the rate of observed survival in DLBCL patients reflects the rate of expected survival in the background population (statistical cure); and second, even if patients do have a late relapse and have a survival outcome that matches the background population, the probability of relapse for any incident cohort peaks at 7 years at around 28-30%. The sponsor considered that to reflect all the groups of patients who would be considered in the non-cured pool (i.e., due to diagnosis, treatment as new case or relapsed, and various modes of monitoring), the affected population would be better reflected using a 10-year limited duration for the prevalence estimate and based on Europe sources only.

Based on these assumptions and the review of the epidemiological data sources found, the sponsor concluded on an average 10-year prevalence for DLBCL of 4.28 per 10,000 persons in the EU.

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

Cancer Registry	**Country/ies**	**Year (latest)**	**Population**	**Prevalence Period Capture**			
				5 years	***10 years***	***20 years***	***Complete / lifetime***
NORDCAN[1]	Denmark, Faroe Islands, Finland, Greenland, Iceland, Norway, Sweden	2019	27,036,000	2.60	4.33	6.88	-
IKLN[2]	The Netherlands	2021	17,172,569	3.09	5.12	7.11	-
Slovania Cancer Registry[3]	Slovania	2018	2,077,837	1.99	3.26	-	4.93
AIRTUM[4]	Italy	2020	60,731,000	-	-	-	7.73
Robert Kock Institut[5]	Germany	2018	82,349,000	2.90	4.78	6.94	7.45
REDECAN[6]	Spain	2020	46,445,000	2.33	-	-	7.55

Belgium Cancer Registry[7]	Belgium	2018	11,430,000	2.34	3.93	-	-
HMRN	United Kingdom	2016	65,610,000	2.63	4.23	-	-
SEER[8]	USA	2018	326,800,000	2.40	3.99	5.74	6.16
EU 27 estimate[9]		***2022***		***2.54***	***4.28***	***6.98***	***6.92***

Sources: Largønningen et al. 2021, IKNL 2021, AIRTUM 2015, SLORA 2021, Robert Koch Institute 2020, REDECAN 2022, Belgium Cancer Registry 2021, HMRN 2021, SEER 2020

1 Based on pooled cancer registry data from seven Nordic countries:Denmark, Faroe Islands, Finland, Greenland, Iceland, Norway, Sweden for 2019 and applying EU weighted average ratio of DLBCL to NHL (35.02%) to the gender specific prevalence proportions for 2019

2 Based on extracting total counted prevalence cases for 2021 for the duration of interest (5 yr = 5313, 10 yr = 8798, 20 yr = 12217), divided by the 2021 population in The Netherlands

3 Based on extracting total counted NHL prevalence cases for 2018 for the duration of interest (5 yr = 414, 10 yr = 678, lifetime = 1026), multiplied by DLBCL to NHL incidence rate ratio for Slovenia in 2018 (29.6%), divided by the 2018 population in Slovenia

4 Based on the number of DLBCL cases reported (n=46751) divided by the 2020 population in AIRTUM registry report for 2020

5 Based on applying German 2018 DLBCL to NHL ratio (37% in 2018) to the total NHL reported prevalence cases in 2018 for each period of capture. Complete/lifetime prevalence is reported as 25 years

6 Based on applying Spanish 2015 DLBCL to NHL ratio (35.5%) to the total NHL reported prevalence cases in 2020 at 5 yrs (n=31,052) and lifetime (n=100,058)

7 Based on extracting total counted prevalence cases for 2018 for the duration of interest (5 yr = 1762, 10 yr =3086), divided by the 2020 population in Belgium

8 SEER registry calculates complete prevalence using 26 year period up to year 2018

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

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

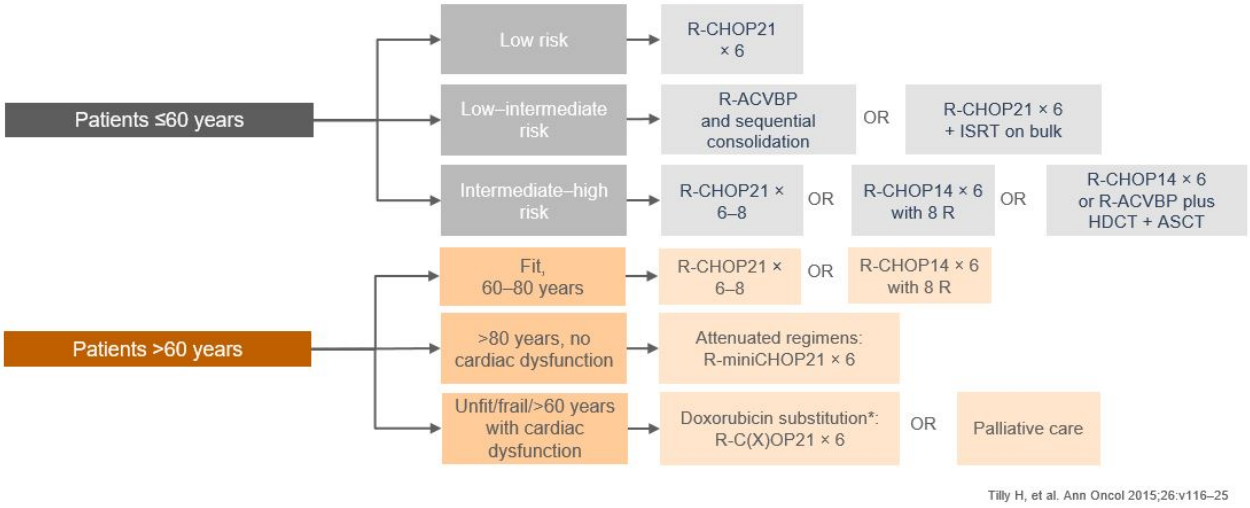
Article 3(1)(b) of Regulation (EC) No 141/2000

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

Existing methods

The sponsor referred to the latest ESMO guidelines for DLBCL, which describe some of the treatment strategies available to these patients in Europe and outlined the current standard of care (SOC) in the first-line setting based on European and American treatment guidelines as summarised below (Tilly et al., 2015; NCCN 2021) (Figure 1). An overview of the existing agents used as part of the regimens in the EU for the treatment of DLBCL was also provided in Table 2. The indications for the approved agents (except for rituximab) among patients in the first-line setting are not specific for DLBCL, but rather for NHL. The ESMO guidelines therefore provide further clarity as to what treatments are used for patients with DLBCL among the approved agents.

Figure 1. ESMO Guidelines: 1L therapy for DLBCL



*With gemcitabine, etoposide or liposomal doxorubicin or others
1L=first line; ACVBP=doxorubicin, vindesine, cyclophosphamide, bleomycin and prednisolone; ASCT=autologous stem-cell transplantation; CHOP=cyclophosphamide, doxorubicin, vincristine, and prednisone; ESMO=European Society for Medical Oncology; HDCT=high-dose chemotherapy; ISRT=involved site radiotherapy; R-CHOP=rituximab and CHOP; R-CHOP14=R-CHOP given every 14 days; R-CHOP21=R-CHOP given every 21 days; R-miniCHOP=reduced dose R-CHOP given every 21 days.

Table 2. Existing agents used as part of treatment regimens for first line (1L) DLBCL in the EU

Compound	Trade Names	Member States Where Authorised	Indication[a]
Bleomycin	Bleo, Bleo-cell, Bleocin, Bleo-Kyowa, Bleomedac, Bleomycin(e), Bleomycin medac, Bleomycin Accord	AT, BE, BG, CZ, DK, EE, DE, EL, FI, FR, LV, LT, LU, NL, PL, PT, RO, SI, SK	Indicated in NHL. In the ESMO guidelines it is recommended for the treatment of 1L DLBCL patients.[b c]
Cyclophosphamide	Cyclophosphamide, Cyclolest, Demacylan, Endoxan(a), Genoxal, Sendoxan	AT, BE, CZ, DK, FI, FR, DE, EE, EL, HR, HU, IE, IT, LU, NL, NO, PL, PT, RO, ES, SE, SI	Indicated in NHL. In addition, it may be used in the treatment of 1L DLBCL as recommended in the ESMO guidelines[b].
Doxorubicin (liposomal)b	Adriblastina-PFS, Caelyx, Doxorubicin Actavis, Doxorubicin-Ebewe, Doxorubicin medac, Doxorubicin Teva, Doxorubicinum Accord, Myocet	EU27	Indicated in NHL. In addition, it may be used in the treatment of 1L DLBCL as recommended in the ESMO guidelines.[b]
Prednisone / prednisolone	There are many different preparations of Prednisone/Prednisolon		Indicated in lymphoma. Prednisone/ prednisolone is used in the treatment of DLBCL as part of the CHOP regimen.

Compound	Trade Names	Member States Where Authorised	Indication[a]
	e on the market having diverse indications.		
Rituximab	Blitzima, MabThera, Ritemvia, Rituzena, Rixathon, Riximyo, Ruxience, Truxima	EU27	Rituximab is indicated for the treatment of patients with CD20 positive diffuse large B-cell non-Hodgkin's lymphoma in combination with CHOP chemotherapy.
Vincristine	Cellcristin, Oncovin, Sindovin, Vincrisin, vincristine, Vincristine Pfizer, Vincristine-Teva, Vincristin-Richter	AT, BE, CY, CZ, DK, FI, FR, DE, EL, HR, IT, LT, LU, NL, PL, PT, RO, SE	Indicated in NHL. In addition, it may be used in the treatment of DLBCL as recommended in the ESMO guidelines[b].
Vindesine	Eldisin(e), Enison, Gesidine	AT, BE, CZ, FI, FR, DE, IE, IT, LU, NL, ES, SE	DLBCL is not listed in the indication of any vindesine-containing products. However, it may be used in the treatment of DLBCL as recommended in the ESMO guidelines[b] [c].
Etoposide	Actavis, Celltop, Ebeposid, Eposin, Etobion, Eto-cell, Eto-Gry, Etomedac, Etopofos, Etopophos, Etoposid Actavis, Etoposid Ebewe, Etoposide Accord, Etoposide Kabi, Etoposide Medac, Etoposide Sandoz, Etoposide Teva, Lastet, Riboposid, Sintopozid, Toposin, Vepesid	AT, BE, CY, CZ, DK, EE, FI, FR, DE, EL, HR, HU, IE, IT, LT, LU, NL, NO, PL, PT, ES, RO, SE, SI	Indicated in NHL. In addition, it may be used in the treatment of DLBCL as recommended in the ESMO guidelines.[b]

Polivy (polatuzumab vedotin) was approved in the EU (Procedure No. EMEA/H/C/004870) on 16-Jan-2020 and is authorised in combination with bendamustine and rituximab for the treatment of adult patients with r/r DLBCL who are not candidates for haematopoietic stem-cell transplantation (SCT).

This extension of the indication for Polivy in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone (R-CHP) is intended to include treatment of adult patients with previously untreated DLBCL in the first-line setting. The sponsor argued that rituximab in combination with cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP) remains the prevailing SOC regimen for the intended patient population. This was supported by efficacy outcomes reported for other regimens compared to R-CHOP. According to the current ESMO guidelines, R-CHOP is considered a satisfactory method of treatment relevant for a discussion on the significant benefit of Polivy in previously untreated DLBCL. The COMP agreed with the sponsor that the only satisfactory method of

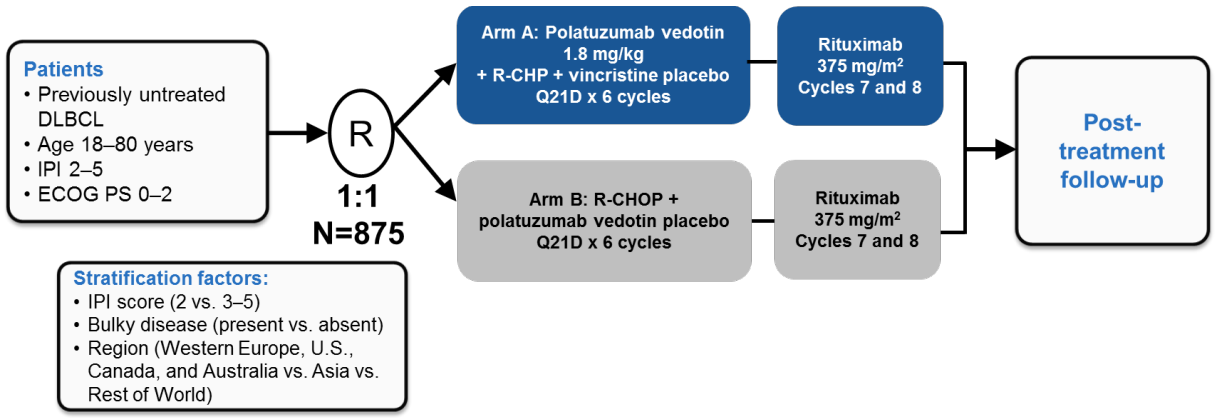
treatment for the target DLBCL population of this new Polivy indication is R-CHOP, the SOC in first line therapy.

Significant benefit

The sponsor argued that polatuzumab vedotin represents an important new therapeutic option for adult patients with previously untreated DLBCL and claimed significant benefit in terms of improved efficacy based on a substantive improvement in both PFS and event-free survival (EFS) over the SOC first line R-CHOP regimen, which has been the SOC for these patients for two decades. The sponsor did not seek protocol assistance for the justification of significant benefit.

The primary data supporting the efficacy and safety of polatuzumab vedotin (pola) in the proposed extension of indication are obtained from a multicenter, randomized, double-blind, placebo-controlled phase 3 study called GO39942 (hereafter referred to as POLARIX). The study is designed to evaluate the efficacy and safety of pola in combination with R-CHP versus R-CHOP in previously untreated patients with DLBCL. A schematic representation of the study design is shown in Figure 2.

Figure 2. Overview of the Design of Study GO39942



DLBCL: diffuse large B-cell lymphoma; ECOG PS: Eastern Cooperative Oncology Group Performance Status; IPI: International Prognostic Index; Q21D: every 21 days; R: randomization; R-CHOP: rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; R-CHP: rituximab plus cyclophosphamide, doxorubicin, and prednisone.

The primary objective of study GO39942 was to evaluate the efficacy of pola+R-CHP compared with R-CHOP with respect to PFS as determined by the investigator. The primary endpoint PFS is defined as the time from randomization to the first occurrence of disease progression or relapse as determined by the investigator, or death from any cause, whichever occurs earlier. Key secondary efficacy endpoints were included in a hierarchical testing procedure in the following order: EFS as determined by the investigator, CR rate at end of treatment by FDG-PET as determined by BICR, and OS.

A reduction in relative risk of disease progression, relapse, or death by 27% was observed in newly diagnosed patients with DLBCL treated in the pola+R-CHP arm (stratified HR: 0.73 [95% CI: 0.57, 0.95]; two-sided log-rank p-value=0.0177, two-sided α=0.05), with a minimum of 24 months from study enrolment in both treatment arms. The results of all sensitivity analyses were consistent with the results of the primary analysis of PFS in the intent-to-treat (ITT) population. Moreover, a significant reduction in the risk of occurrence of disease by 25% was observed in patients treated in the pola+R-

CHP arm compared to patients treated in the R-CHOP arm (stratified HR: 0.75 [95% CI: 0.58, 0.96, p=0.0177]).

The sponsor emphasised that the pivotal phase 3, comparative study POLARIX met its primary efficacy endpoint and demonstrated a statistically significant PFS improvement with the combination of polatuzumab vedotin and R-CHP over R-CHOP in the ITT population, inclusive of the high-risk subpopulations with poor prognostic factors. The study design stipulated that all patients were followed for at least 24 months after treatment initiation, which covers the period when most of the disease relapses occur, thus ensuring that the observed treatment benefits of polatuzumab vedotin are reliable, particularly with respect to the primary endpoint of PFS. At the 2-year mark, treatment with polatuzumab vedotin plus R-CHP resulted in a higher proportion of patients alive and progression-free compared to R-CHOP (76.7% versus 70.2%, respectively). Consistent with the study results on the primary endpoint, in the randomized comparison, polatuzumab vedotin plus R-CHP showed a statistically significant improvement in the formally tested key secondary efficacy endpoint EFS.

The COMP concluded that the results from the pivotal, comparative study POLARIX can justify the claim of significant benefit of the combination of polatuzumab vedotin and R-CHP based on improved PFS and EFS over the well-established SOC regimen R-CHOP for adult patients with previously untreated DLBCL.

4. COMP position adopted on 25 March 2022

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan condition of the designated Orphan Medicinal Product.
- the prevalence of diffuse large B-cell lymphoma (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be 4.3 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is chronically debilitating due to constitutional symptoms, local symptoms of lymphadenopathy, end-organ damage from disease involvement, and bone marrow failure that may lead to infections, anaemia, and thrombocytopenia, and life-threatening in patients not responding to treatment;
- although satisfactory methods for the treatment of the condition have been authorised in the European Union, the assumption that Polivy may be of potential significant benefit in patients with previously untreated diffuse large B-cell lymphoma still holds. This is based on an improvement in progression free survival and event free survival when Polivy is used in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone (R-CHP) as compared to standard of care regimen (R-CHOP). The COMP considered that the product offers a clinically relevant advantage.

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

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

The Committee for Orphan Medicinal Products has recommended that Polivy, polatuzumab vedotin, for treatment of diffuse large B-cell lymphoma (EU/3/18/2013) is not removed from the Community Register of Orphan Medicinal Products.