17 July 2024
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EMADOC-1700519818-1622761
Committee for Orphan Medicinal Products

Orphan designation withdrawal assessment report

Ordspono (odronextamab)

Sponsor: Regeneron Ireland Designated Activity Company

Note

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

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1. Introductory comment

The marketing authorisation of Ordspono was associated with two orphan designations in the following conditions:

- Treatment of follicular lymphoma (EU/3/22/2649)
- Treatment of diffuse large B-cell lymphoma (EU/3/22/2656)

The two separate assessments of the maintenance of the orphan designation criteria are covered in this document. Of note, the sponsor of the two orphan designations for Ordspono withdrew both orphan designations prior to COMP final opinion.

2. Ordspono (odronextamab) EU/3/22/2649

2.1. Product and administrative information

Product	
Designated active substance	Odronextamab
Other name	Ordspono
International Non-Proprietary Name	Odronextamab
Tradename	-
Orphan condition	Treatment of follicular lymphoma
Sponsor's details:	Regeneron Ireland Designated Activity Company One Warrington Place Dublin 2 D02 HH27 Ireland
Orphan medicinal product designation procedural history	
Sponsor/applicant	Regeneron Ireland Designated Activity Company
COMP opinion	16 June 2022
EC decision	18 July 2022
EC registration number	EU/3/22/2649
Post-designation procedural history	
Rapporteur / Co-rapporteur	Filip Josephson / Karin Janssen van Doorn
Applicant	Regeneron Ireland Designated Activity Company
Application submission	26 July 2023
Procedure start	17 August 2023
Procedure number	EMA/H/C/006215/0000
Invented name	Ordspono
Approved therapeutic indication	Ordspono as monotherapy is indicated for the treatment of adult patients with relapsed or refractory follicular lymphoma (r/r FL) after two or more lines of systemic therapy Further information can be found in the European public assessment report (EPAR) on the Agency's website: www.ema.europa.eu/en/medicines/human/EPAR/Ordspono
CHMP opinion	27 June 2024
COMP review of orphan medicinal product designation procedural history	
COMP rapporteurs	Maria Elisabeth Kalland / Bozenna Dembowska-Baginska
Sponsor's report submission	26 February 2024
COMP discussion and adoption of list of questions	18-20 June 2024
Oral explanation	17 July 2024
Sponsor's removal request	17 July 2024

2.2. Grounds for the COMP opinion

The COMP opinion that was the basis for the initial orphan medicinal product in 16 June 2022 designation was based on the following grounds:

- the intention to treat the condition with the medicinal product containing odronextamab was considered justified based on preliminary clinical data which showed responses in patients with relapsed or refractory follicular lymphoma;
- the condition is life-threatening and chronically debilitating due to lymphadenopathy, splenomegaly, bone marrow dysfunction, and the potential of transformation to aggressive lymphoma;
- the condition was estimated to be affecting approximately 4.9 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 odronextamab will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that showed complete responses in a high proportion of previously treated patients with relapsed or refractory follicular lymphoma who have failed several lines of approved therapies. 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 odronextamab as an orphan medicinal product for the orphan condition: treatment of follicular lymphoma.

2.3. 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

Follicular lymphoma (FL) represents the second most common subtype of non-Hodgkin's lymphoma (NHL), and the most common indolent NHL (iNHL), and constitutes about 20–25% of all new cases of NHL in western countries (Swerdlow et al., 2017). It is a mature B-cell lymphoproliferative disorder of transformed germinal center B-cells, consisting of a mixture of centrocytes (small to medium-sized cleaved follicular center cells) and centroblasts (large non-cleaved follicular center cells), that typically involves a follicular growth pattern for most of the cases (85%) (Alaggio et al., 2022; Smith et al., 2013; Xerri et al., 2016). This subtype of FL is now termed classic FL (cFL), and harbour the t(14;18)(q32;q21) translocation associated with IGH::BCL2 fusion and overexpression of cytoplasmic B-cell leukaemia/lymphoma 2 (BCL2) protein. This type is separated from two related subtypes, specifically follicular large B-cell lymphoma (FLBL) and FL with uncommon features (uFL) (Alaggio et al., 2022).

FL includes a high degree of mutational and clinical heterogeneity, ranging from an indolent to a highly aggressive clinical course with a frequent need for several lines of treatment (Qualls et al., 2022). The World Health Organization (WHO) classification has earlier adopted a grading from 1-3, where grade 3 has been subdivided into grade 3a, in which centrocytes are present, and grade 3b, in which there are sheets of centroblasts (Ott et al., 2002). The clinical aggressiveness of FL increases with increasing numbers of centroblasts, and subsequently grades. FL grade 1-3a comprises the most prevalent indolent (low-grade) lymphoma subtype of NHL. In contrast, FL grade 3b, which largely equals to the recently defined subtype of FLBL, is at an intermediate stage of large cell transformation and is typically treated as an aggressive (high-grade) lymphoma (Alaggio et al., 2022; Dreyling et al., 2021; Swerdlow et al., 2017). The grading of FL, which is only pertinent to cFL, is no longer mandatory according to the latest revision of the WHO classification (Alaggio et al., 2022).

The aetiology of FL is still poorly understood. It has been suggested that age, gender, and ethnicity may affect a person's likelihood of developing FL. The incidence increases with age; although in principle FL may occur at any age, it is extremely rare in children and adolescents. The median age at diagnosis of FL is around 60-65 years. Although onset can be gradual at the time of initial diagnosis, advanced FL is typically incurable, and the response rates are lower with shorter durations of response with successive lines of therapy (Jacobsen, 2022).

The approved therapeutic indication "Ordspono as monotherapy is indicated for the treatment of adult patients with relapsed or refractory follicular lymphoma (r/r FL) after two or more lines of systemic therapy" falls within the scope of the designated orphan condition "treatment of follicular lymphoma".

Intention to diagnose, prevent or treat

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

Chronically debilitating and/or life-threatening nature

Patients with FL generally present with asymptomatic lymphadenopathy, with waxing and waning symptoms present for years. Most patients therefore have widespread disease at diagnosis, including peripheral and central (abdominal and thoracic) lymphadenopathy and splenomegaly. Approximately 10% of the patients have localized disease at diagnosis and less than 20% present with B symptoms (fever, night sweats and weight loss) and elevated serum lactate dehydrogenase (LDH) levels. The bone marrow is involved in around 40-70% of the cases, whereas involvement of other normal organs in extra-nodal sites is uncommon (Swerdlow et al., 2017; Freedman, 2020). Signs related to bone marrow involvement such as anaemia, leukopenia, or thrombocytopenia are rare at presentation but can be observed in the later stages of the disease.

The majority (> 70%) of patients with FL present in an advanced stage. (Gupta G et al, Am J Blood Res 2022;12(4):105-124). Patients with advanced stage FL disease may experience B symptoms (present in about 20% of patients) and suffer from unexplained fatigue/asthenia, local effects of lymphadenopathy such as abdominal pain, chest pain, cough or dyspnoea, or symptoms of bone marrow failure leading to cytopenia. Patients with relapsed disease may have a reduced quality of life.

The sponsor discussed the life-threatening nature of the disease stating that the median survival of patients with FL vary depending on identified molecular and clinical risk factors. It is estimated that approximately 30% of patients experience disease progression within 24 months (POD24) of front-line therapy, which is a well-known predictor of a poor prognosis (Casulo et al., 2022), and that the 5-year overall survival (OS) rate is markedly lower in these patients compared to those without early progression (50% vs. 90%, respectively) (Casulo et al., 2016). Although life expectancy has improved due to recent therapeutic advances, FL patients frequently relapse and become progressively more refractory to subsequent lines of therapy. Advanced-stage FL is considered incurable with conventional chemotherapy, although patients often have good responses to treatment and might live for several years. The survival outcome worsens significantly as the patients progress through multiple lines of therapy and most patients eventually die of progressive lymphoma and its complications (Link et al., 2019). Moreover, histologic transformation to high-grade NHLs that are clinically more aggressive with a poor outcome is relatively common in FL patients, occurring at a rate of approximately 2-3% per year (Kridel et al., 2016; Freedman, 2018).

The sponsor has not identified any significant changes in the severe nature of the condition since the orphan designation in 2022. FL remains life-threatening and chronically debilitating, mainly due to lymphadenopathy, splenomegaly, bone marrow dysfunction, and the potential of transformation into aggressive lymphoma.

Number of people affected or at risk

At the time of the orphan designation in 2022, the COMP concluded that the condition was estimated to be affecting approximately 4.9 in 10,000 persons in the European Union (EU).

The sponsor proposed a prevalence of 4.8 per 10,000 persons.

The sponsor has conducted an updated comprehensive review of published studies to determine the current prevalence of FL in the EU. Published data from population-based cancer registry databases and other relevant sources including the European Cancer Information System (ECIS; 2022) database, the International Agency for Research on Cancer's (IARC)'s Global Cancer Observatory (GCO, formerly GLOBOCAN; 2020), European Cancer Registry-based Study on Survival and Care of Cancer Patients (EUROCARE; 1997-2008), Surveillance of Rare Cancers in Europe (RARECARE; 27 EU member states [EU27] +UK [EU28], 2008), Cancer Registry based Project on Haematologic Malignancies

(HAEMACARE; 2000-2002), Association of Nordic Cancer Registries (NORDCAN; Denmark, Faroe Islands, Finland, Greenland, Iceland, Norway, and Sweden; 2021), Netherlands Cancer Registry (NCR; The Netherlands, 2020), Swedish Lymphoma Registry (SLR; Sweden, 2020), the German cancer registry Robert Koch Institute (Germany; 2019), the national Slovenian Cancer Registry (SCR; Slovenia; 2019), Spanish Network of Cancer Registries (REDECAN; Spain; 2020), and Italian Association of Cancer Registries (AIRTUM; Italy, 2020) were searched. In addition, a comprehensive literature search on PubMed (2010 to present) was conducted in November 2023. The Eurostat database (EC, 2023) was used as the source of the updated total population data.

Prevalence estimates (both limited-duration prevalence and complete prevalence) reported by population-based registries (i.e., direct method) were found in published reports by NCR, AIRTUM, NORDCAN, SCR, REDECAN, and Robert Koch Institute. To comprehensively incorporate all available sources of data on FL prevalence, the direct estimates were supplemented with prevalence estimates derived through an indirect method using the estimated FL incidence and disease duration.

The sponsor presented the FL prevalence as reported by population-based cancer registries, including national registries in the Netherlands, Italy, for seven Nordic countries or territories (NORDCAN), Slovenia, Spain, and Germany. It was emphasised that since FL is an incurable disease, the complete prevalence is considered the most relevant prevalence period. The best prevalence estimates for the EU27 using the direct method was therefore calculated to **4.33 per 10,000** people in 2023.

For the calculation of incidence of FL as a proportion of NHL the sponsor refereed to ECIS which reports the crude incidence of NHL for the EU in 2022 (most recent estimate available) as 2.08/10,000 person-years (PY). The percentage of NHL cases diagnosed with FL was estimated using data published by population-based cancer registries in the EU. The proportion of FL among incident NHL cases (i.e., % FL/NHL) varied across countries, ranging from 9.9% in Poland to 22.4% in Austria. Sensitivity analyses were performed with varying assumptions for estimating the pooled average of published incidence data on FL and NHL in the EU countries. The average **proportion** for FL/NHL including data from HAEMACARE was estimated to 16.3% (a total of 26,586 FL patients out of 163,330 incident NHL patients). Applying 16.3% of incident NHL as FL, the sponsor estimated the incidence of FL in the EU to be 2.08/10,000 PY x 16.3% = 0.34/10,000 PY.

For the disease duration, four studies using population-based cancer registries reported median or 10-year OS of FL. One study in the Netherlands among 234 FL patients (diagnosed between 1981-1989) reported a median OS of 5.8 years; one study in Sweden among 2,641 FL patients reported 10-year OS of 51% in 2000-2002 and 59% in 2003-2010, corresponding to estimated median OS of 10.2 and 12.2 years; one study in France among 384 FL patients (diagnosed between 1980-2009) reported a median OS of 13 years; another study among 1,074 grade 1-3a FL patients in Spain reported a median OS of approximately 20 years. However, the survival reported by the latter study was considered overestimated as it only included younger patients with FL grade 1-3a (with 58% aged ≤60 years at diagnosis) from a single clinic centre in Barcelona. Based on the findings from the literature review, the sponsor concluded that the maximum reported median OS for FL in 2020 is approximately 14 years in the European community.

As supportive evidence, the sponsor also examined data from the Surveillance, Epidemiology, and End Results (SEER) database of the National Cancer Institute (NCI), an authoritative source of information on cancer epidemiology in the US which reports a median OS of 13.8 years for FL patients diagnosed between 2000-2018. The SEER median survival of 13.8 years supports the estimated median OS of 14.0-years derived from EU data, which can be viewed as a conservative upper limit for the EU.

Given the limited number of publications reporting the median OS for FL, the sponsor reviewed relative survival (RS) estimates from large population-based cancer registries. The 5-year RS rates were consistent across various studies, supporting the external validity of the median OS of 13 years reported by Dandoit (Dandoit et al., 2015) and a similar estimate of 12.2 years derived from the study reported by Junlén and colleagues (Junlén et al, 2014). Additionally, the sponsor used these data to estimate a maximum average disease duration of approximately 14 years in the EU, which was then used for the primary analysis without further sensitivity testing.

Based on the review of the epidemiological data sources found and the above-mentioned assumptions, the sponsor concluded on a complete prevalence estimate for FL of 0.34/10,000PY x 14.0Y = 4.76 per 10,000 or, after rounding, 4.8 per 10,000 people in the EU.

The sponsor conducted two sensitivity analyses on FL prevalence using the indirect method, based on the proportion of FL among all incident NHL cases using 1) studies with all diagnosed on or after 2000, and 2) the same studies as for the first analysis, but excluding HAEMACARE data. The cut-off from 2000 was chosen to balance the recency of the data and the number of studies available. The % FL/NHL was estimated at 15.4% initially, resulting in a prevalence of 4.5 per 10,000 people. Excluding HAEMACARE data increased the % FL/NHL to 17%, with a prevalence estimate of 4.9 per 10,000 people in the EU. The sponsor noted that the estimate without HAEMACARE was considered less representative of the EU, given that HAEMACARE covered 30% of the European population.

According to the sponsor, the sensitivity analyses confirmed the robustness of the proposed estimate. Of the three estimates presented, the primary indirect estimate of 4.8 per 10,000 people was the preferred estimate because it was more geographically representative of the EU population than the upper conservative sensitivity estimate. The sponsor indicated that the FL prevalence has not changed since the orphan designation for odronextamab was granted in 2022.

The proposed prevalence is consistent with recent considerations accepted in orphan designations and maintenances of the status that have been granted for FL in the EU from 2021 to 2023. In these cases, the prevalence of FL has been concluded to be approximately 4.8-4.9 per 10,000 people in the European community. These estimates were calculated using ECIS data for the crude incidence of NHL, a weighted average proportion of FL within all NHL in the community of either 16.3% (Kanas et al., 2022), 16.5%, or ~18-20%, and a disease duration of 14.5-15 years for most of the considerations and 16.3 years for the latest orphan maintenance procedure for FL (Yescarta; EMA/OD/0000068456). The COMP considered that the same conclusion as for the orphan designation can therefore be accepted for this procedure, that FL affects approximately 4.9 in 10,000 people in the EU.

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

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

Existing methods

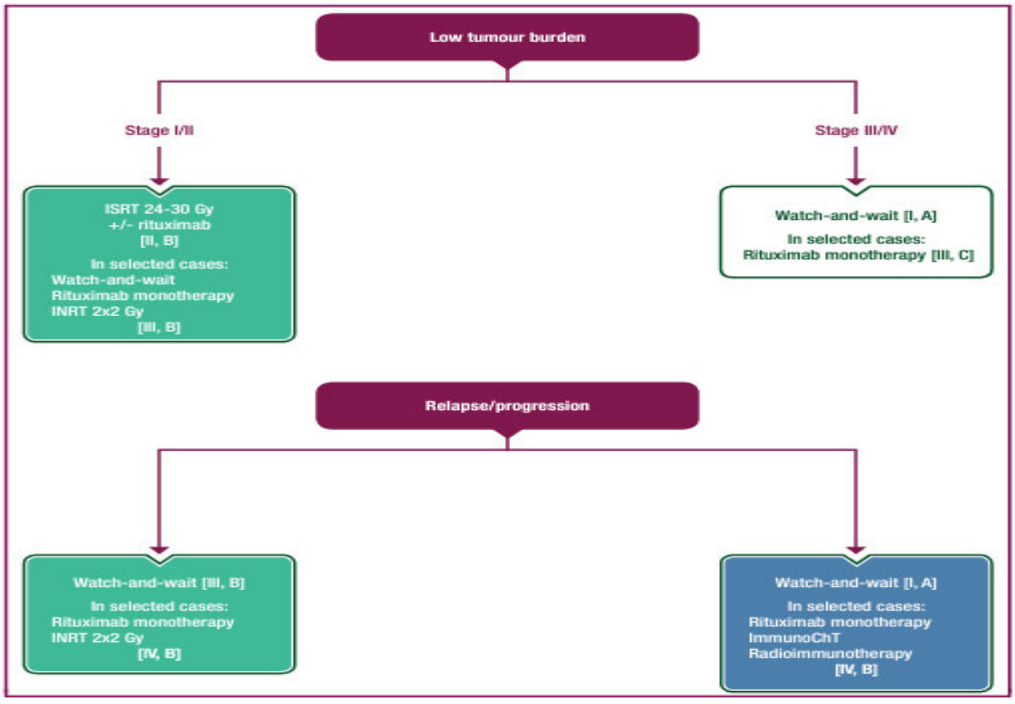
The sponsor described the treatment methods available to patients with FL based on the most recent European society for medical oncology (ESMO) treatment guidelines for these patients (Dreyling et al., 2021), and the medicines approved after its publication in 2021. The treatment of patients with newly diagnosed FL generally depends on tumour burden, patient age, and disease stage. There is significant heterogeneity between patients in the use of treatment and responses to treatment, with the latter being a key determinant of a patient's overall prognosis (Kahl 2016). In patients with FL without

significant comorbidities, the combination of anti-CD20 antibody (obinutuzumab or rituximab) with chemotherapy (e.g., bendamustine; cyclophosphamide, doxorubicin, vincristine, prednisone; or cyclophosphamide, vincristine, prednisone) is considered standard of care in first-line treatment. For patients who are elderly and considered unfit for the above regimens, treatment options include rituximab alone, chlorambucil or cyclophosphamide with or without rituximab. Patients who progress after one line of therapy may consider other standard regimens used in frontline treatment based on their performance status.

After initial treatment, most patients with FL relapse, and when they do, treatment is typically with therapies that include an anti-CD20 antibody (e.g., bendamustine plus obinutuzumab or rituximab, and lenalidomide with or without rituximab). Factors that guide the selection of a particular regimen include prior anti-lymphoma therapy, duration of first remission, the grade of the FL, and whether the patient is fit to receive chemotherapy or not. For later relapses, monotherapy with palliative intent may be considered (for example idelalisib which has been approved for double-refractory FL) and among younger patients with a high-risk profile or among patients who relapse after autologous stem cell transplantation (ASCT), allogeneic stem cell transplantation may be a treatment option. Further, guidelines acknowledge innovative medicines such as CAR-T cell therapies but note that toxicities associated with these treatments may limit their use to relapsing patients with poor prognostic features (Dreyling et al., 2021).

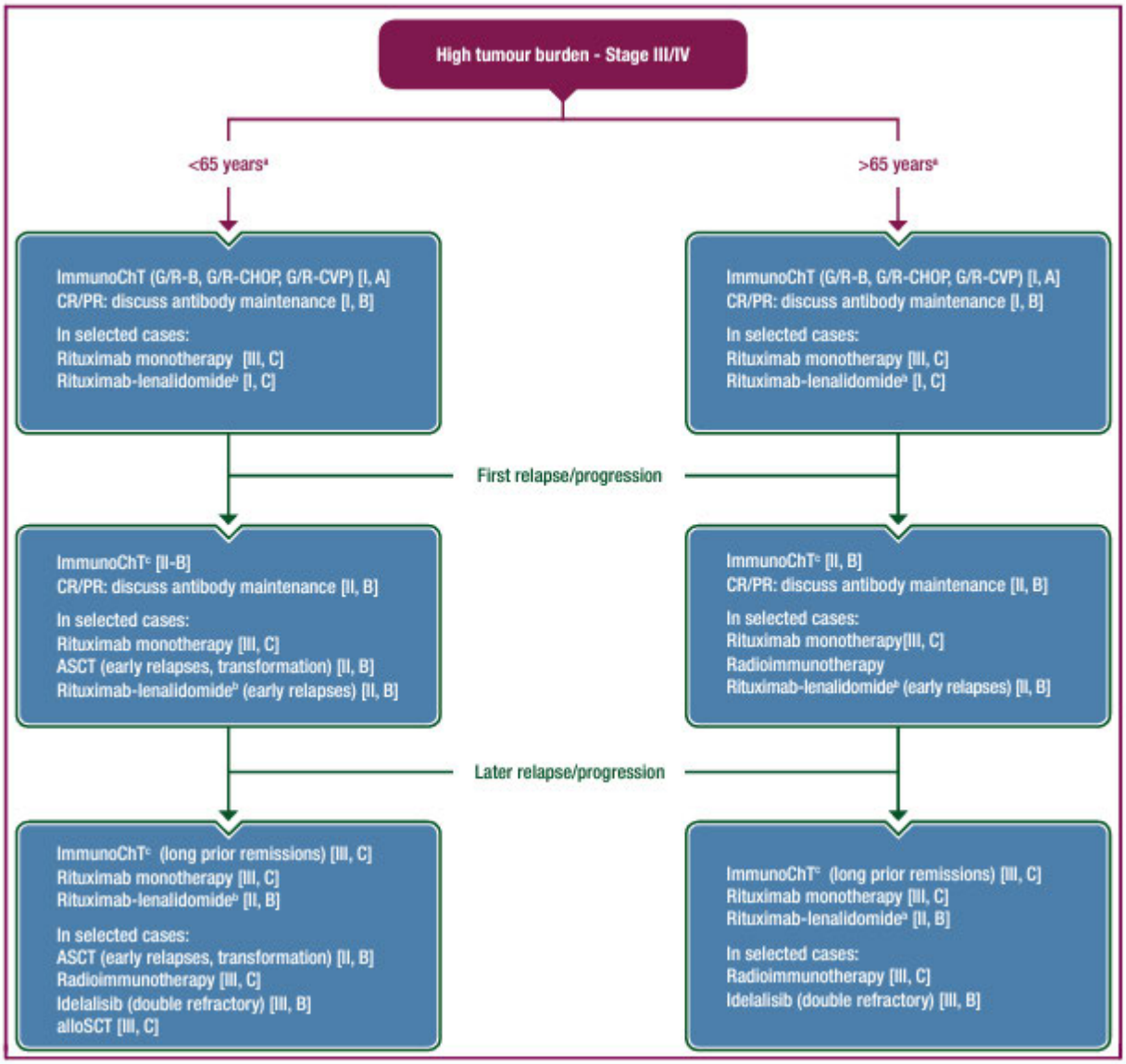
According to the ESMO guidelines, therapy should be initiated only upon development of symptoms. The clinical treatment guidelines identify two types of FL populations that are offered two different treatment algorithms depending on their tumour burden, being either low (Figure 1) or high (Figure 2).

Figure 1. Treatment algorithm for FL patients with low tumour burden



ChT, chemotherapy; FL, follicular lymphoma; INRT, involved-node radiotherapy; ISRT, involved-site radiotherapy.

Figure 2. Treatment algorithm for FL patients with high tumour burden



alloSCT, allogeneic stem cell transplantation; ASCT, autologous stem cell transplantation; B, bendamustine; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisolone; ChT, chemotherapy; CR, complete response; CVP, cyclophosphamide, vincristine, prednisolone; FL, follicular lymphoma; G, obinutuzumab; PR, partial response; R, rituximab. a Biological age (years). b Off-label. c Preferred in rituximab-refractory cases.

The sponsor's product odronextamab is intended to treat adults with r/r FL after two or more lines of systemic therapy. An overview of medicinal products authorised for treatment of relapsed FL in the EU and whether they are considered satisfactory methods of treatment relevant for a discussion on the significant benefit of odronextamab in FL is presented in the Table 1 below.

In summary, the approved indications for tisagenlecleucel (Kymriah), mosunetuzumab (Lunsumio), and zanubrutinib (Brukinsa) are covering the therapeutic indication proposed for odronextamab and are therefore considered to be satisfactory methods relevant for a discussion on the significant benefit of odronextamab in the target FL population. The other medicines have more restricted indications as compared to that applied for odronextamab and will not be further discussed.

Table 1. Medicinal products authorised for the treatment of r/r FL in the EU

Product (INN),	Procedure #, Approval Date and Type of MA	Mechanism of Action (MoA)	Therapeutic indication per SmPC	Considerations regarding satisfactory methods
Zevalin ([90Y] (ibritumomab tiuxetan)	EMEA/H/C/000547 16 Jan 2004 Full MA	CD20 monoclonal antibody with radioisotopes	[90Y]-radiolabelled Zevalin is indicated as consolidation therapy after remission induction in previously untreated patients with FL [90Y]-radiolabelled Zevalin is indicated for the treatment of adult patients with rituximab relapsed or refractory CD20+ follicular B-NHL	Not applicable since the marketing authorization for Zevalin has been expired
Zydelig (idelalisib)	EMEA/H/C/003843 18 Sep 2014 Full MA	PI3K inhibitor	Zydelig is indicated as monotherapy for the treatment of adult patients with FL that is refractory to two prior lines of treatment	Not a satisfactory method; covers only FL patients who are refractory to at least two prior systemic therapies
Gazyvaro (obinutuzumab) plus bendamustine	EMEA/H/C/002799 13 Jun 2016 Full MA	CD20 antibody + bendamustine	Gazyvaro in combination with bendamustine followed by Gazyvaro maintenance is indicated for the treatment of patients with FL who did not respond or who progressed during or up to 6 months after treatment with rituximab or a rituximab-containing regimen	Not a satisfactory method; only indicated for patients with rituximab-refractory FL
Revlimid (lenalidomide) plus rituximab	EMEA/H/C/000717 18 Dec 2019 Full MA	CD20 antibody + lenalidomide	Revlimid in combination with rituximab (anti-CD20 antibody) is indicated for the treatment of adult patients with previously treated FL (Grade 1 – 3a)	Not a satisfactory method ; only indicated for patients with r/r FL grade 1-3a*
Copiktra (duvelisib)	EMEA/H/C/005381 19 May 2021 Full MA	PI3K inhibitor	Copiktra monotherapy is indicated for the treatment of adult patients with FL that is refractory to at least two prior systemic therapies.	Not a satisfactory method; covers only FL patients who are refractory to at least two prior systemic therapies
Kymriah (tisagenlecleucel)	EMEA/H/C/004090 29 Apr 2022 Full MA	Anti-CD19 CAR-T	Kymriah is indicated for the treatment of adult patients with r/r FL after two or more lines of systemic therapy	Satisfactory method; complete overlap with the proposed therapeutic indication of odronextamab
Lunsumio (mosunetuzumab)	EMEA/H/C/005680 03 Jun 2022 CMA	CD20xCD3 bispecific antibody	Lunsumio as monotherapy is indicated for the treatment of adult patients with r/r FL	Satisfactory method; complete overlap with the proposed

Product (INN),	Procedure #, Approval Date and Type of MA	Mechanism of Action (MoA)	Therapeutic indication per SmPC	Considerations regarding satisfactory methods
			who have received at least two prior systemic therapies	therapeutic indication of odronextamab
Yescarta (axicabtagene ciloleucel)	EMEA/H/C/004480 21 Jun 2022 Full MA	Anti-CD19 CAR-T	Yescarta is indicated for the treatment of adult patients with r/r FL after three or more lines of systemic therapy	Not a satisfactory method: covers only patients who have failed three or more lines of systemic therapy
Brukinsa (zanubrutinib) plus obinutuzumab	EMEA/H/C/004978 22 Nov 2021 Full MA	BTK inhibitor	Brukinsa in combination with obinutuzumab is indicated for the treatment of adult patients with r/r FL)who have received at least two prior systemic therapies.	Satisfactory method; complete overlap with the proposed therapeutic indication of odronextamab

MoA: Mode of action
CMA: Conditional marketing authorisation
MA: Marketing authorisation
* Since grade 3b FL biologically is more closely related to DLBCL than to the other forms of FL, these patients are often treated as an aggressive lymphoma such as DLBCL, for which Ordspono will be authorised. Ordspono will be intended for FL without any grade-relevant restrictions, since an extrapolation of the positive B/R balance of Ordspono observed in the studied FL grade 1-3a and DLBCL populations to patients with FL grade 3b can be considered acceptable. The label of Ordspono is thus for all grades of FL.

Significant benefit

The sponsor did not seek any protocol assistance from EMA to get advice on a suitable approach for collecting the evidence needed to justify significant benefit over existing methods of treatment for patients with r/r FL who have received at least two prior lines of systemic therapy. However, prior to the granting of the orphan designation, the sponsor received scientific advice on the clinical development plan of odronextamab in FL.

Odronextamab is an anti-CD20/CD3 human IgG4-based bispecific antibody therapy, thereby being a T-cell engager that recognizes the T-cell antigen CD3 and the B-cell antigen CD20, a proven target for the treatment of FL. The sponsor claimed that odronextamab in monotherapy has demonstrated a significant benefit based on a clinically relevant advantage in terms of improved efficacy and better safety profile compared to existing therapies for patients with r/r FL in the third- and later lines setting.

The claim of significant benefit is based on the results from an ongoing, open-label, multi-centre, multi-cohort, single-arm phase 2 study 1625, which is used to obtain the pivotal evidence for odronextamab as monotherapy in patients (≥18 years) with r/r FL grade 1-3a who have received at least two prior lines of systemic therapy in the conditional marketing authorisation (CMA) application. The study consisted of 5 disease-specific B-cell NHL cohorts: FL, DLBCL, mantle cell lymphoma (MCL), marginal zone lymphoma (MZL), and other B-NHL (containing aggressive B-NHL subtypes not included in the other 4 cohorts). Patients who had received prior treatment with any CAR-T therapy and an anti-CD20/CD3 bispecific therapy were excluded from the study. The efficacy data consisted of 128 evaluable patients (defined as patients with or who had the opportunity for response assessment at 12 weeks) from the FL cohort of the study. The data cut-off (DCO) date for the updated efficacy and safety analyses provided was 20-Oct-2023. At the DCO, the median duration of study follow-up was 20.1 months (range: 17.3, 28.7) for the FL cohort.

Among the 128 patients with r/r FL in Study 1625, the median age was 61 years (range: 22 to 84), 38% were age 65 or older, 53% were male, 62% were White, 27% were Asian, 51% with ECOG performance status (PS) 0, and 48% with ECOG PS 1. The median number of prior therapies was 3 (range 2 to 13), 72% of patients had disease that was refractory to the last line of therapy, 74% were refractory to an anti CD20 antibody in an earlier line of therapy, and 42% were double refractory (to anti CD20 antibody and alkylating agents) in any line of therapy. Fourteen percent of patients had received a prior PI3K inhibitor, 13% had received prior lenalidomide in combination with rituximab, 26% had a Follicular Lymphoma International Prognostic Index (FLIPI) score of 2 (intermediate) and 58% had a FLIPI score of 3 to 5 (high), 14% had bulky disease, 49% had progression of disease within 24 months (POD24), and 30% had prior ASCT.

The primary objective of study 1625 is to evaluate the antitumor activity of odronextamab as a single agent as measured by objective response rate (ORR) according to the Lugano classification criteria (Cheson et al., 2014) in each of the B-NHL subgroups, including patients with FL grade 1-3a who have relapsed after or are refractory to at least two prior lines of systemic therapy, including an anti-CD20 antibody and an alkylating agent. The primary endpoint ORR, which is assessed by an independent review committee (IRC), is defined as the best overall response (BOR) of a partial response (PR) or complete response (CR) which is achieved within 52 weeks after receiving the first dose. Secondary endpoints included duration of response (DOR), CR rate (CRR), duration of complete response (DOCR), time to response (TTR), progression-free survival (PFS), and OS. The results are presented in the table below.

Table 2. Efficacy results in patients with r/r FL

Efficacy endpoints	**Ordspono** **(N=128)**
Objective response rate % (n) (95% CI)	80% (103) (73, 87)
Complete response (CR) rate, % (n) (95% CI)	73% (94) (65, 81)
Partial response (PR) rate, % (n) (95% CI)	7% (9) (3, 13)
Duration of Response (DOR)[a]	N=103
Patients with event, % (n)	42% (43)
Median, months (95% CI)	23 (18, NE)
Duration of Complete Response (DOCR)[b]	N=94
Patients with event, % (n)	38% (36)
Median, months (95% CI)	25 (20, NE)

CI=confidence interval; K-M=Kaplan-Meier; NE=not evaluable.
[a] DOR is defined as the time from the initial occurrence of a documented PR or CR until the patient experiences an event (documented disease progression or death due to any cause, whichever occurs first).
[b] DOCR is defined as the time from the initial occurrence of a documented CR until the patient experiences an event (documented disease progression or death due to any cause, whichever occurs first).

The first response assessment occurred at 12 weeks. The median time to first response was 2.7 months (range: 1.8 to 7.9 months) and the median time to first complete response was 2.7 months (range: 2.3 to 7.9 months).

Significant benefit of odronextamab over tisagenlecleucel (Kymriah)

The sponsor claimed significant benefit of odronextamab over tisagenlecleucel based on improved efficacy and improved safety. According to the sponsor, complementary to the mechanism of action (MoA) of tisangenlecleucel, odronextamab offers an effective treatment option with a different MoA and targets a different tumour associated antigen (TAA) than CD19 which is the target of the approved CAR-T cell therapy for FL.

The efficacy and safety of tisagenlecleucel in r/r FL patients was evaluated in the registrational study ELARA (NCT03568461) (Dreyling et al., 2022; Fowler et al., 2022) (Table 3).

Table 3. Key characteristics of patients with r/r FL in clinical studies with odronextamab and tisagenlecleucel

	Odronextamab	**Tisagenlecleucel**
Study	R1979-ONC-1625	ELARA
Reference/ data cut-off date	Oct 2023 data cut-off	Fowler, 2022
N	N=128	N=97[a]
POD24	63 (49.2)	61 (62.9)
Refractory to last LoT	92 (71.9)	76/97 (78.4)
Prior LOTs, median (range)	3 (2–13)	4 (2–13)
# of prior LOTs: 1	0	0/94 (0)
# of prior LOTs: 2	59 (46.1)	24/94 (25.5)
# of prior LOTs: ≥3	69 (53.9)	70/94 (74.5)
ECOG 0	65 (50.8)	53/94 (56.4)
ECOG 1	62 (48.4)	38/94 (40.4)
ECOG 2	1 (0.8)	3/94 (3.2)[b]
FLIPI Low risk: 0–1	21 (16.4)	18 (18.6)
FLIPI Intermediate risk: 2	33 (25.8)	20 (20.6)
FLIPI High risk: 3–5	74 (57.8)	58 (59.8)
Age, median (range)	61 (22–84)	57 (29–73)
≥65 years	49 (38.3)	24 (24.7)
Ann Arbor disease stage I–II	19 (14.8)	14/97 (19.6)
Ann Arbor disease stage III–IV	109 (85.2)	83/97 (85.6)
Ann Arbor disease stage III	42 (32.8)	26/98 (26.53)
Ann Arbor disease stage IV	67 (52.3)	57/98 (59.18)
Double-refractory	54 (42.2)	66/97 (68.0)

a. Baseline data were reported for 97 infused patients unless indicated separately, efficacy and safety outcomes reported for 94 and 97 patients respectively (Canadian Agency for Drugs and Technologies in Health. CADTH Reimbursement Review: Tisagenlecleucel-Kymriah 2023.)
b. Some patients had ECOG PS of 2 recorded just before receiving tisagenlecleucel infusion, and not at the time of signing the informed consent form.

In general, ELARA had a higher proportion of patients with POD24 (62.9% vs. 49.2%), refractory to last line of therapy (78.4% vs. 71.9%) and ≥3 prior lines of therapy (74.5% vs. 53.9%)) compared to patients in the r/r FL cohort of study 1625. However, a higher proportion of patients who were treated with odronextamab were ≥ 65 years of age compared to tisagenlecleucel (38.3% vs. 24.7%).

Response outcomes observed in patients with r/r FL who were treated with odronextamab in study 1625 and tisagenlecleucel in ELARA have been presented in Table 4.

Table 4. Response outcomes to odronextamab and tisagenlecleucel in patients with r/r FL

	Odronextamab	**Tisagenlecleucel**
Study	R1979-ONC-1625	ELARA
Reference/ Data cut-off	Oct 2023 data cut-off	Kymriah SmPC 2023 Dreyling 2022
ORR: % (n/N) (95% CI)	80.5% (103/128) (72.5% to 86.9%)	Enrolled patients (n=98) 85.7% (84/98) (95% CI not reported) Efficacy analysis set (n=94) 86.2% (81/94) (77.5%, 92.4%)
CR rate: % (n/N) (95% CI)	73.4% (94/128) (64.9% to 80.9%)	Enrolled patients (n=98) 68.4% (67/98) (58.2%, 77.4%) Efficacy analysis set (n=94) 69.1% (65/94) (58.8%, 78.3%)

Tisagenlecleucel demonstrated ORR of 85.7% and CRR of 68.4% (Dreyling 2022) which were similarly high compared to odronextamab [ORR: 80.5%, CRR: 73.4%]. Even in high-risk subgroup of patients including POD24 and refractory to last line of therapy which had higher representation in ELARA compared to study 1625, responses rates in terms of CRR of odronextamab were similarly high compared to tisagenlecleucel [POD24: 73.0% vs. 59%; refractory to last prior therapy: 71.7% vs. 68.9%, respectively] (Fowler, 2022).

Although the time between leukapheresis and availability of the manufactured tisagenlecleucel therapy can range between 3 to 4 weeks, a recent meta-analysis estimated the median time between leukapheresis and tisagenlecleucel infusion to be 49 days (range, 32 to 64 days) (Jacobson, 2023).

Treatment emergent adverse events (TEAEs) [grade ≥3: 78.4% (76/97)] and serious TEAEs [43.3% (42/97)] were reported for patients receiving tisagenlecleucel. Mostly low-grade cytokine release syndrome (CRS) [(any grade: 49.5% (48/97), grade ≥3: 1% (1/97)] was reported and neurological adverse reactions were observed in 11.3% patients, including 3% grade ≥3 immune effector cell-associated neurotoxicity syndrome (ICANS). For odronextamab, TEAEs of CRS any grade was 58.2% (46/79 patients who received 0.7/4/20mg step-up regimen) and grade 3 CRS was reported for one patient [1.3% (1/79)] and no grade 4/5 CRS was reported. Odronextamab had a lower rate of ICANS (one patient experienced grade 2 ICANS) compared to tisagenlecleucel. Although TEAEs of infection [any grade: 78.4% (120/153), grade 3+: 40.5% (62/153)] were higher for odronextamab compared to tisagenlecleucel (any grade: 50%, grade 3+: 16%), the risk of infection is adequately managed by risk mitigation guidance.

Additionally, CAR-T cell therapies may not be suitable for all patients with r/r FL due to the increased risk of secondary malignancies (Verdun and Marks, 2023) which requires life-long monitoring. Reports from clinical trials and/or post-marketing AE data sources have recently led to health authority investigations into the risk of T-cell malignancy with serious outcomes, including hospitalization and death (EMA/PRAC/545005/2023 Jan 2024; FDA Safety and Availability communication 2023).

In summary, odronextamab has favourable efficacy data among higher risk patients and an older study population and has lower rates of ICANS compared to tisagenlecleucel. Additionally, the increased risk of secondary malignancies associated with CAR-T cell therapies and the generally manageable safety and tolerability profile of odronextamab further contribute to the significant benefit of odronextamab over tisagenlecleucel for the treatment of patients with r/r FL.

COMP discussion

In terms of improved efficacy, tisagenlecleucel showed responses which were similar compared to those reported for odronextamab (ORR: 85.7% vs. 80.5%, CRR: 68.4% vs. 73.4%). These figures do not indicate any differences in terms of efficacy based on descriptive cross-study comparisons.

The COMP considered that given the limited experience with odronextamab from a single-arm study with limited follow-up, the claim of better safety in comparison to tisagenlecleucel cannot be concluded on at present stage and no adequate quantification is possible with the proposed indirect comparisons presented.

In conclusion, the COMP considered that the sponsor should submit a matching-adjusted indirect comparisons of the efficacy outcomes, including the duration of responses, between patients treated with tisagenlecleucel in ELARA versus those treated with odronextamab in study 1625. In addition, the sponsor should submit the reported best responses and duration of the responses as achieved with odronextamab for those patients, if anyone, from relevant clinical studies who were pre-treated with tisagenlecleucel prior to study entry (if available).

Significant benefit of *odronextamab over mosunetuzumab (Lunsumio)*

The efficacy and safety of mosunetuzumab in r/r FL patients was evaluated in the registrational multi-centre, single-arm, phase 1/2 dose escalation and dose-expansion study GO29781 (N=90) (Budde et al., 2022). The FL cohort from the dose expansion part of study GO29781 received the registrational dose of mosunetuzumab. The sponsor claimed significant benefit of odronextamab over mosunetuzumab based on improved efficacy and improved safety. Key baseline and clinical characteristics of patients in the efficacy eligible r/r FL population from study 1625 and study GO29781 have been summarised in Table 5.

Table 5. Key characteristics of patients with r/r FL in clinical studies with odronextamab and mosunetuzumab

	Odronextamab	**Mosunetuzumab**
Study	R1979-ONC-1625	GO29781
Reference/ Data cut-off	Oct 2023 data cut-off	Budde, 2022
N	N=128	N=90
POD24	63 (49.2)	47 (52.2)
Refractory to last LoT	92 (71.9)	62 (68.9)
Prior LOTs, median (range)	3 (2–13)	3 (2–10)
# of prior LOTs: 1	0	0
# of prior LOTs: 2	59 (46.1)	34 (37.8)
# of prior LOTs: ≥3	69 (53.9)	56 (62.2)
ECOG 0	65 (50.8)	53 (58.9)
ECOG 1	62 (48.4)	37 (41.1)
ECOG 2	1 (0.8)	0 (0) ¶
FLIPI Low risk: 0–1	21 (16.4)	26 (28.9)
FLIPI Intermediate risk: 2	33 (25.8)	24 (26.7)
FLIPI High risk: 3–5	74 (57.8)	40 (44.4)
Age, median (range)	61 (22–84)	60 (29–90)
≥65 years	49 (38.3)	30 (33.3)
Ann Arbor disease stage I–II	19 (14.8)	21 (23.3)
Ann Arbor disease stage III–IV	109 (85.2)	69 (76.7)

	Odronextamab	Mosunetuzumab
Ann Arbor disease stage III	42 (32.8)	25 (27.8)
Ann Arbor disease stage IV	67 (52.3)	44 (48.9)
Double-refractory	54 (42.2)	48 (53.3)
Prior stem-cell transplant	39 (30.5)	19 (21.1)

Notes: ¶Imputed assuming no missing data

The r/r FL cohort of study 1625 with odronextamab has 40% more patients compared to the efficacy analysis set of mosunetuzumab's registrational study and hence better represents various subgroups that are associated with poor prognosis or that are relevant for routine clinical practice in the treatment of r/r FL. In general, a higher proportion of patients in the r/r FL cohort of study 1625 had high risk features including FLIPI score 3-5 (57.8% vs. 44.4%), Ann Arbor disease stage III/IV (85.2% vs. 76.7%), and prior stem-cell transplant (30.5% vs. 21.1%) compared to GO29781. Patients in GO29781 had higher proportion of double-refractory patients (53.3% vs. 42.2%) but included more patients with an ECOG PS of 0 (58.9% and 50.8%) compared to study 1625.

As described in Table 6, mosunetuzumab demonstrated similar ORR (80%) but lower CRR (60%) compared to odronextamab (ORR: 80.5%, CRR: 73.4%).

Table 6. Response outcomes to odronextamab and mosunetuzumab in patients with r/r FL

	Odronextamab	Mosunetuzumab
Study	R1979-ONC-1625	GO29781
Reference/ Data cut-off	Oct 2023 data cut-off	Lunsumio SmPC 2023
ORR: % (n/N) (95% CI)	80.5% (103/128) (72.5% to 86.9%)	80% (72/90) (70.3%, 87.7%)
CR rate: % (n/N) (95% CI)	73.4% (94/128) (64.9% to 80.9%)	60% (54/90) (49.1%, 70.2%)

The sponsor argued that given the large magnitude of difference in CRR, odronextamab offers the highest probability of delaying disease progression or death compared to mosunetuzumab. The probability of being alive and progression-free was higher for odronextamab compared to mosunetuzumab (12-month: 66.2% vs. 57.7%; 18-month: 57.5% vs. 47.0%). This claim is further discussed for several subgroups of patients with high-risk features, however, the results stem from a rather limited, single-arm study where the subgroup analysis is not powered, and the time-dependent endpoints are difficult to contextualise.

In addition, several patients with very low or no detectable cluster of differentiation (CD)20 expression in a subgroup analysis (n=70) were able to achieve a CR to odronextamab. According to the sponsor, responses were observed across all levels of CD20 expression and may indicate that odronextamab could exert anti-tumour activity even in tumours with very low or no CD20 expression. They further argued that the results showed significant benefit over mosunetuzumab based on clinically meaningful responses with odronextamab across patient subgroups with all levels of CD20 expression.

In terms of safety outcomes associated with T-cell engager therapies, the sponsor also argued that patients treated with odronextamab had a lower rate of high-grade CRS compared to those who received mosunetuzumab (CRS grade ≥3: 1.3% [1/79] vs. 3.3% [3/90]), although the AEs of CRS were higher for odronextamab (any grade CRS: 58.2% [46/79] vs. 45.6% [41/90]). (EMA, Lunsumio

EPAR, 2022). On the contrary, TEAEs of infection were higher for patients treated with odronextamab compared to those treated with mosunetuzumab (any grade: 78.4% vs. 51.1% [46/90]; grade ≥3: 40.5% vs. 16.7% [15/90]). However, it was emphasised that the risk of infection associated with odronextamab is adequately managed by risk mitigation guidance.

COMP conclusion

The claim of improved efficacy of odronextamab over mosunetuzumab is not considered established based on the data provided. Odronextamab showed similar ORR (80.5%) and CRR (73.4%) compared to mosunetuzumab [ORR (80%) and CRR (60%)]. These figures do not indicate any differences in terms of efficacy based on descriptive cross-study comparisons.

In addition, the argument of improved safety based on the frequencies of overlapping toxicities in terms of CRS does not reflect the whole picture and biases due to differences in patient characteristic cannot be excluded. Given the limited experience with odronextamab from a small single-arm study with limited follow-up, the claim of a better safety profile in comparison to mosunetuzumab cannot be concluded on at present stage and no adequate quantification is possible for the descriptive cross-study comparisons presented.

In conclusion, the descriptive data provided do not support the claim of significant benefit of odronextamab over mosunetuzumab in patients with r/r FL in the third- and later lines setting.

The COMP considered that the sponsor should submit a matching-adjusted indirect comparisons of the efficacy outcomes, including the duration of responses, between patients treated with mosunetuzumab in study GO29781 versus those treated with odronextamab in study 1625. In addition, the sponsor should submit the reported best responses and duration of the responses as achieved with odronextamab for those patients in the pivotal study 1625, if anyone, who were pre-treated with Lunsumio before study entry.

Significant benefit of odronextamab over zanubrutinib (Brukinsa)

The safety and efficacy of zanubrutinib in combination with obinutuzumab was evaluated in the phase 2 study ROSEWOOD in which patients with r/r FL who had received ≥2 lines of therapy, including an anti-CD20 therapy and an alkylating agent, were randomly assigned in a 2:1 ratio to zanubrutinib plus obinutuzumab or obinutuzumab (Zinzani et al., 2023). The sponsor claimed significant benefit of odronextamab over zanubrutinib based on improved efficacy and improved safety. The key baseline characteristics of patients in the zanubrutinib in combination with obinutuzumab arm of the ROSEWOOD study are presented in Table 7.

Table 7. Key characteristics of patients with r/r FL in the clinical studies with odronextamab and zanubrutinib in combination with obinutuzumab

Baseline variables	**Odronextamab**	**Zanubrutinib + Obinutuzumab**
Study	R1979-ONC-1625	ROSEWOOD
Reference/ Data cut-off	Oct 2023 data cut-off	Zinzani, 2023
N	N=128	N=145 (arm of Z+O)
POD24	63 (49.2)	50 (34.4)
Refractory to last LoT	92 (71.9)	47 (32.4)
Prior LOTs, median (range)	3 (2–13)	3 (2-11)
# of prior LOTs: 1	0	0¶
# of prior LOTs: 2-3	84 (65.6)	104 (71.7)
# of prior LOTs: >3	44 (34.4)	41 (28.2)
Serum LDH> ULN	53 (41.4)	49 (33.8)
ECOG 0	65 (50.8)	86 (59.3)

Baseline variables	Odronextamab	Zanubrutinib + Obinutuzumab
ECOG 1	62 (48.4)	54 (37.2)
ECOG 2	1 (0.8)	5 (3.4)
FLIPI Low/intermediate risk: 0–2	54 (42.1)	68 (46.9)¶
FLIPI High risk: 3–5	74 (57.8)	77 (53.1)
Age, median (range)	61 (22–84)	63.0 (31-84)
≥65 years	49 (38.3)	62 (42.8)
Ann Arbor disease stage I–II	19 (14.8)	26 (17.9)¶
Ann Arbor disease stage III–IV	109 (85.2)	119 (82.1)
Double-refractory	54 (42.2)	--
Notes: ¶Imputed assuming no missing data (denominator =145)		

In general, the efficacy analysis set of study 1625 for odronextamab had more patients with features associated with poor prognosis including POD24 (49.2% vs. 34.4%), refractory to last line of therapy (71.9% vs. 32.4%), >3 prior lines of therapy (34.4% vs. 28.2%), and ECOG PS of 1-2 (49.2% vs. 40.7%) compared to zanubrutinib in combination with obinutuzumab in the ROSEWOOD study.

Despite a more severe population for those treated with odronextamab in study 1625, ORR and CRR were higher for odronextamab compared to zanubrutinib in combination with obinutuzumab as described in Table 8.

Table 8. Response outcomes to odronextamab and zanubrutinib in combination with obinutuzumab in clinical studies with r/r FL patients

	Odronextamab	Zanubrutinib in combination with obinutuzumab
Study	R1979-ONC-1625	ROSEWOOD
Reference/ Data cut-off	Oct 2023 data cut-off	Brukinsa SmPC 2023
ORR: % (n/N) (95% CI)	80.5% (103/128) (72.5% to 86.9%)	69.0% (100/145) (60.8%, 76.4%)
CR rate: % (n/N) (95% CI)	73.4% (94/128) (64.9% to 80.9%)	CR 39.3% (57/145) (not reported)

The sponsor also noted that TEAEs of high-grade neutropenia (grade ≥3: 11.2% vs. 28.1% [43/153]) and thrombocytopenia (grade ≥3: 9.8% vs. 3.3% [5/153]) were reported for zanubrutinib in combination with obinutuzumab as well as for odronextamab. Although TEAEs of infections were higher for odronextamab (any grade: 78.4% vs. 58.0% [83/143]; grade ≥3: 40.5% vs. 31.5% [45/143]) compared to zanubrutinib in combination with obinutuzumab, it was argued that the risk of infections associated with odronextamab can be adequately managed by risk mitigation guidance.

In summary, the sponsor claims that odronextamab has a manageable safety and tolerability profile and has demonstrated higher ORR and markedly higher CR in a more severe patient population thereby demonstrating a significant benefit over zanubrutinib in combination with obinutuzumab.

COMP discussion

The reported efficacy outcomes from the two clinical studies indicated that patients with r/r FL treated with odronextamab in study 1625 achieved a higher CRR and ORR compared to patients treated with zanubrutinib in combination with obinutuzumab in ROSEWOOD. Specifically, the CRR of odronextamab was 1.9-fold higher than that reported for zanubrutinib in combination with obinutuzumab (73% vs.

39%). The ORR was also numerically higher (81% vs. 69%) although the durability of the ORR could not be compared as the median DOR was not reached at a comparable study follow-up time between the two studies, which was 20.2 months in the zanubrutinib plus obinutuzumab combination arm.

In conclusion, the indirect comparison of efficacy data from the two pivotal single-arm studies 1625 and ROSEWOOD could support the claim for significant benefit of odronextamab based on better efficacy in terms of durable responses which were higher and deeper compared to zanubrutinib in combination with obinutuzumab in r/r FL patients in the third- and later lines setting.

Overall COMP conclusions

The claim of significant benefit based on a clinically relevant advantage for odronextamab (Ordspono) over the combination regimen with zanubrutinib (Brukinsa) plus obinutuzumab can be considered established based the descriptive side-by-side comparisons of the efficacy outcomes for odronextamab in study 1625 as compared to those reported for zanubrutinib in the ROSEWOOD study. However, the claim of significant benefit of odronextamab over tisagenlecleucel (Kymriah) and mosunetuzumab (Lunsumio) in adult patients with r/r FL in the third- and later lines setting is not considered established based on the data provided. The sponsor should therefore further discuss the arguments for significant benefit over these two products for the target patient population and based on supplementary data.

2.4. COMP list of issues

The claim of significant benefit of odronextamab over the authorised satisfactory methods Kymriah and Lunsumio for the target patient population is not considered established based on the data presented. The sponsor should therefore provide supplementary information with regards to:

- The reported best responses and duration of the responses as achieved with odronextamab for those patients in the pivotal study 1625 or any other relevant studies, if anyone, who were pre-treated with each of the two satisfactory methods, Kymriah and Lunsumio, separately.
- The relative efficacy of odronextamab versus each of the two products using matching-adjusted indirect comparisons of the efficacy outcomes, including the duration of responses, between patients treated with Kymriah in ELARA and Lunsumio in GO29781 versus patients treated with odronextamab in study 1625.

3. Ordspono (odronextamab) EU/3/22/2656

3.1. Product and administrative information

Product	
Designated active substance	Odronextamab
Other name	Ordspono
International Non-Proprietary Name	Odronextamab
Tradename	-
Orphan condition	Treatment of diffuse large B-cell lymphoma
Sponsor's details:	Regeneron Ireland Designated Activity Company One Warrington Place Dublin 2 D02 HH27 Ireland
Orphan medicinal product designation procedural history	
Sponsor/applicant	Regeneron Ireland Designated Activity Company
COMP opinion	16 June 2022
EC decision	18 July 2022
EC registration number	EU/3/22/2656
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Filip Josephson / Karin Janssen van Doorn
Applicant	Regeneron Ireland Designated Activity Company
Application submission	26 July 2023
Procedure start	17 August 2023
Procedure number	EMA/H/C/006215/0000
Invented name	Ordspono
Approved therapeutic indication	Ordspono as monotherapy is indicated for the treatment of adult patients with relapsed or refractory diffuse large B cell lymphoma (r/r DLBCL) after two or more lines of systemic therapy Further information can be found in the European public assessment report (EPAR) on the Agency's website: www.ema.europa.eu/en/medicines/human/EPAR/Ordspono
CHMP opinion	27 June 2024
COMP review of orphan medicinal product designation procedural history	
COMP rapporteurs	Maria Elisabeth Kalland / Bozenna Dembowska-Baginska
EMA scientific officer	Kyriaki Tzogani
Expert	-
Sponsor's report submission	26 February 2024
COMP discussion and adoption of list of questions	18-20 June 2024
Oral explanation	17 July 2024

Sponsor's removal request	17 July 2024

3.2. Grounds for the COMP opinion

The COMP opinion that was the basis for the initial orphan medicinal product in 2022 designation was based on the following grounds:

- the intention to treat the condition with the medicinal product containing odronextamab was considered justified based on preliminary clinical data showing durable responses achieved in patients with relapsed/refractory diffuse large B-cell lymphoma;
- the condition is chronically debilitating due to involvement of single or multiple nodal or extranodal sites, including the gastrointestinal tract, the central nervous system and bone marrow and life-threatening in patients with relapsed/refractory disease;
- the condition was estimated to be affecting approximately 4.3 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 odronextamab will be of significant benefit to those affected by the condition. The sponsor has provided clinical data which demonstrated durable responses in heavily pre-treated patients with relapsed/refractory diffuse large B-cell lymphoma. 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 odronextamab as an orphan medicinal product for the orphan condition: treatment of diffuse large B-cell lymphoma.

3.3. 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 the most common subtype of non-Hodgkin's lymphoma (NHL) in adults. The disease comprises a group of fast-growing, aggressive lymphoid malignancies that accounts for around 30-40% of all NHL cases globally (Chaganti et al.,2016). This rare blood cancer is histologically characterised by dense proliferation of large, transformed mature B-cells with prominent nucleoli and basophilic cytoplasm, which typically express the pan B-cell antigens CD19, CD20, CD22, CD79a, as well as other surface markers characteristic for the B-cell lineage (Martelli et al., 2013). In

addition to occurring de novo, DLBCL can arise through the transformation from different types of low-grade B-cell malignancy such as follicular lymphoma (FL), marginal zone lymphoma (MZL), or chronic lymphocytic leukaemia (Richter's transformation).

DLBCL is a heterogeneous B-cell neoplasm that includes tumours arising from germinal centre B-cells (GCB) and post-germinal centre B-cells. The 2016 World Health Organization (WHO) classification of lymphoid neoplasms recognizes germinal centre B-cell-like (GCB) and activated B-cell-like (ABC) as two subtypes of DLBCL with different prognosis with current therapies (Swerdlow et al., 2016). The molecular pathogenesis of DLBCL is complex and includes both genetic lesions that are relatively specific for this disease (i.e., rearrangements of B-cell lymphoma 6 [BCL6]) and molecular alterations that are shared with other NHL variants. Most tumours have rearrangement of the immunoglobulin heavy and light chain genes and somatic mutations of the variable regions of these genes. MYC gene rearrangement is seen in 5-15% of DLBCL and is frequently associated with BCL2, and to a lesser extent with BCL6. Large cell lymphomas with MYC and BCL2 and/or BCL6 rearrangements are included in a separate category in the 2016 WHO classification. In the 5th edition of the WHO classification of haematolymphoid tumours with a focus on lymphoid neoplasms (WHO-HAEM5) from 2022, this has been re-categorised as DLBCL/ high-grade B-cell lymphoma (HGBL) associated with MYC and BCL2 rearrangements, while the MYC/BCL6 double hit lymphomas are now considered genetic subtypes of DLBCL, not otherwise specified (NOS) or of HGBL, NOS (Alaggio et al., 2022).

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

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

Intention to diagnose, prevent or treat

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

Chronically debilitating and/or life-threatening nature

The sponsor discussed the life-threatening nature of the disease with a cure rate for patients with newly diagnosed aggressive B-cell lymphoma, such as DLBCL, of approximately 50% with standard chemoimmunotherapy (Coiffier, 2005). Prognosis for patients with r/r DLBCL has historically been poor, with a 4-year overall survival (OS) rate of 47% in patients who experienced disease relapse within 12 months from initial diagnosis and 13% in patients with a transient or no response (whose disease is refractory) to initial therapy (Farooq, 2017).

The sponsor also discussed that the clinical course of DLBCL can be debilitating due to constitutional symptoms such as fever, night sweats, weight loss, local symptoms of lymphadenopathy such as pain, disfigurement, end-organ damage from disease involvement, and bone marrow failure that may lead to infections, anaemia, and thrombocytopenia (Armitage 1998; Cheson 2014). Despite improved survival with immunochemotherapy, patients often experience significant toxic effects such as nausea, emesis, infections, mucositis, bleeding, peripheral neuropathy, and organ damage from the chemotherapy

resulting in poor quality of life (Pfreundschuh 2008; Oerlemans 2014; van der Poel 2014). In addition, patients with r/r disease experience decreased response rates and shortened responses with each successive line of therapy.

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

Number of people affected or at risk

At the time of the orphan designation in 2022, the COMP concluded that the condition was estimated to be affecting approximately 4.3 in 10,000 persons in the European Union (EU).

The sponsor has conducted an updated comprehensive review of published studies to determine the current prevalence of DLBCL in the EU. Published data from population-based cancer registry databases and other relevant sources including the interactive web-based ECIS (2022) database, the International Agency for Research on Cancer's (IARC)'s Global Cancer Observatory (GCO, formerly GLOBOCAN; 2020), European Cancer Registry-based Study on Survival and Care of Cancer Patients (EUROCARE; 2008), Surveillance of Rare Cancers in Europe (RARECARE; 27 EU member states [EU27] +UK [EU28], 2008), Cancer Registry based Project on Haematologic Malignancies (HAEMACARE; 2000-2002), Association of Nordic Cancer Registries (NORDCAN; Nordic countries: Denmark, Faroe Islands, Finland, Greenland, Iceland, Norway, and Sweden; 2021), Netherlands Cancer Registry (NCR; The Netherlands, 2020), Swedish Lymphoma Registry (SLR; Sweden, 2020), the German cancer registry Robert Koch Institute (Germany; 2019), the national Slovenian Cancer Registry (SCR; Slovenia; 2019), Spanish Network of Cancer Registries (REDECAN; Spain; 2020), and Italian Association of Cancer Registries (AIRTUM; Italy, 2020) were searched. In addition, a comprehensive literature search on PubMed (2010 to present) was conducted in November 2023. The Eurostat database (EC, 2023) was used as the source of the updated total population data.

Prevalence estimates (both limited-duration prevalence and complete prevalence) reported by population-based registries (i.e., direct method) were found in published reports by NCR, AIRTUM, NORDCAN, SCR, REDECAN, and Robert Koch Institute. To comprehensively review the available sources of data on DLBCL prevalence, the direct estimates were supplemented with prevalence estimates derived through an indirect method using the estimated DLBCL incidence and disease duration. Incidence of DLBCL was estimated based on the most recently reported crude incidence of NHL by ECIS in 2022 and the proportion of patients diagnosed with DLBCL among incident NHL cases as reported in the literature. Disease duration was estimated using median OS reported in literature.

The prevalence of DLBCL as reported by population-based cancer registries, including national registries in the Netherlands, Italy, for seven Nordic countries or territories (NORDCAN), Slovenia, Spain, and Germany are presented in Table 9. The sponsor proposed that the 10-year limited duration prevalence is the most relevant for estimating the prevalence of active DLBCL in the EU as published evidence have shown that the cumulative relapse for DLBCL peaks around 6-8 years and plateaus afterwards (Maurer et al., 2014; Harrysson et al., 2021). The best prevalence estimates for the EU27 in 2023 using the direct method is thus that calculated to 4.27 per 10,000 people.

Table 9. Published prevalence of DLBCL (per 10,000) in the EU countries from population-based cancer registries

			Prevalence Period[a]			
Database, Country/Region	**Year (latest)**	**Population[b] (2023)**	**5 years**	**10 years**	**20 years**	**Complete / lifetime**
The Netherlands Cancer Registry (NCR), the Netherlands[c]	2020	17,811,291	2.85	4.60	6.29	-
AIRTUM, Italy	2020	58,850,717	2.17[d]	-	-	7.84[e]
NORDCAN[f]	2021	27,894,922	2.61	4.38	-	7.08
Slovenia Cancer Registry, Slovenia	2019	2,116,792	3.60[g]	-	-	6.72[h]
REDECAN, Spain	2020	48,059,777	2.14[i]	-	-	6.89[j]
Robert Koch Institute, Germany[k]	2019	84,358,845	2.50	4.17	6.03	-
EU 27 estimate[l]	**2023**		**2.40**	**4.27**	**6.08**	**7.33**

a. Limited-duration prevalence represents the proportion of people alive on a certain day who had a diagnosis of the disease within the past x years (e.g. x = 5, 10 or 20 years). Complete prevalence represents the proportion of people alive on a certain day who were diagnosed with the disease, regardless of how long ago the diagnosis was made.
b. Jan. 1, 2023 population estimates from EUROSTAT (accessed Nov. 20, 2023)
c. Based on extracting total counted prevalence cases for 2020 (most recent non-provisional available) for the duration of interest (5 yr = 4,969; 10 yr = 8,015; 20 year = 10,950), divided by the 2020 population in the Netherlands (n=17,407,585 from EUROSTAT)
d. Calculated by multiplying Italy 2020 DLBCL to NHL prevalence ratio (46,751/156,364 = 29.9%) by the GLOBOCAN 2020 5-year prevalence of NHL (7.27/10,000)
e. Based on the number of DLBCL cases reported in Italy in 2020 (n=46,751) divided by the 2020 population (n=59,641,488 from EUROSTAT)
f. Based on pooled cancer registry data from seven Nordic countries/territories: Denmark, Faroe Islands, Finland, Greenland, Iceland, Norway, and Sweden for 2019 and applying EU-weighted ratio of DLBCL to NHL (34.0%) to the NHL limited duration prevalence per 10,000 for different periods as of 2021 (5 yr = 7.67, 10 yr = 12.89, 20 yr = 20.82)
g. Calculated by multiplying Slovenia 2019 DLBCL to NHL ratio (38.2%) by the GLOBOCAN 2020 5-year prevalence of NHL (9.43/10,000)
h. Calculated by multiplying Slovenian 2019 DLBCL to NHL ratio (38.2%) to the total NHL reported prevalence cases in 2019 (n=3,663), divided by the 2019 population in Slovenia (n=2,080,908 from EUROSTAT)
i. Calculated by multiplying Spanish 2020 DLBCL to NHL ratio (733/2,250 =32.6%; Solans 2019) by the GLOBOCAN 2020 5-year prevalence of NHL (5.61/10,000)
j. Calculated by multiplying Spanish 2020 DLBCL to NHL ratio (733/2,250 =32.6%; Solans 2019) by the total NHL reported prevalent cases in 2020 (n=100,058), divided by the 2020 population in Spain (n=47,332,614 from EUROSTAT)
k. Calculated by applying the German DLBCL to NHL ratio (32.4%) to the NHL limited duration prevalence per 10,000 for different periods as of 2019 (5 yr = 7.71, 10 yr = 12.87, 20 yr = 18.62)
l. EU 27 population-based weighted estimate for countries with reported prevalence estimates, with weights based on 2023 population size.g. Calculated by multiplying Slovenia 2019 DLBCL to NHL ratio (38.2%) by the GLOBOCAN 2020 5-year prevalence of NHL (9.43/10,000)

The most recent NHL crude incidence estimate for the EU population of 2.08 per 10,000 person-years (PY) in 2022 was obtained from ECIS. The sponsor considered the 2022 estimate to be a reasonable approximation of the current incidence rate of NHL in the EU, given that the incidence rates have stabilised in recent years in Europe (Miranda-Filho et al., 2019).

The sponsor estimated the proportion of NHL cases diagnosed with DLBCL using data published by population-based cancer registries in the EU. The HAEMACARE project reported DLBCL accounts for 24.1% of NHL during 2000-2002 which is lower than what was reported by population-based cancer registries from individual EU countries. The proportion of DLBCL among incident NHL cases varied across countries, ranging from 30.4% in Spain to 49.5% in Austria. The sponsor assumed in the analysis that the proportion of DLBCL among NHL cases remained stable over time and included all data published between January 2000 to January 2022 (with cases diagnosed between 1981-2021) to derive the estimation. Sensitivity analyses were performed with varying assumptions for estimating the pooled average of published incidence data on DLBCL and NHL in the EU countries. The average proportion for DLBCL/NHL was estimated to 34.0%. Applying 34.0% of incident NHL as DLBCL, the sponsor estimated the incidence of DLBCL in the EU to be 2.08/10,000PY x 34.0% = 0.71/10,000PY.

The sponsor used published values for the median OS of DLBCL, to approximate the disease duration in the EU. The most recent published data on survival of DLBCL from EUROCARE based on data of 65,995 DLBCL patients diagnosed between 2000-2007 (De Angelis et al., 2015) showed a slight improvement in survival compared to the 5-year relative survival (RS) reported among patients diagnosed between 1992-2002 (Marcos-Gragera et al., 2011). Another study, also using data from EUROCARE showed that the 5-year RS in patients diagnosed with DLBCL in Europe had increased from 1997-1999 to 2006-2008, with variations seen across regions (Sant et al., 2014).

More recent survival estimates were reported by regional cancer registries. In Girona, Spain, 5-year relative survival (RS) increased from 52.1% (2003-2008) to 55.4% (2009-2015), with a 5-year overall survival (OS) of 44.6%, indicating a median OS under 5 years. A recent report from population-based cancer registries in France reported a 5-year OS of 51% (2010-2015) (Monnereau, 2021). The Swedish Lymphoma Registry reported a 5-year OS of 65.3% for curative treatment and a median OS of 2.9 months for non-curative cases (2007-2014) (Harrysson et al., 2021). Overall, DLBCL survival has modestly improved, with a median OS estimated at 5-6 years, which was rounded up to 6 years to be conservative. As supportive evidence, the sponsor reviewed data from the SEER database of the National Cancer Institute representing about 30% of the US population. SEER data from DLBCL patients diagnosed between 2000-2018, reported a median OS of 5.6 years. The sponsor highlighted that this median survival supports the estimated 6-year median OS derived from EU data, reinforcing it as a conservative upper limit for the EU.

Based on the review of the epidemiological data sources found and the above-mentioned assumptions, the sponsor concluded on a complete prevalence estimate for DLBCL of 0.71/10,000PY x 6Y = 4.26 per 10,000 or, after rounding up, 4.3 per 10,000 people in the EU.

The sponsor conducted two sensitivity analyses on DLBCL prevalence using the indirect method. The first analysis, including all cases diagnosed from 2000 and after, estimated a DLBCL prevalence of 3.9 per 10,000 people. The second analysis, excluding HAEMACARE data, estimated a higher prevalence of 4.6 per 10,000 people. The cut-off from 2000 was chosen to balance the recency of the data and the number of studies available. The sponsor noted that the estimate without HAEMACARE data was considered less representative of the EU, given its 30% coverage of the European population.

According to the sponsor, the sensitivity analyses estimated DLBCL prevalence in the EU for 2023 to be between 3.9 and 4.6 per 10,000 people. It was noted that the indirect prevalence estimate, using median OS as a proxy for mean disease duration, may be less accurate since survival exceeds disease duration in curable cases. Consequently, the direct estimate of 4.3 per 10,000 people for the 10-year limited duration was preferred because it more accurately reflects current DLBCL prevalence in the EU. The sponsor indicated that the DLBCL prevalence has not changed since the orphan designation for odronextamab was granted in 2022.

The proposed prevalence is consistent with the prevalence figures recently accepted by the COMP for DLBCL, in addition to be identical to the value accepted at the time of the initial orphan designation. In recent considerations, the COMP has agreed that a 10-year limited duration estimate best reflect the whole DLBCL population and should be used in the calculation since the cumulative relapse for DLBCL has been reported to peak at around 6-8 years and plateau thereafter (Maurer et al., 2014; Harrysson et al., 2021). The same conclusion as for the orphan designation can therefore be accepted for this procedure, that DLBCL affects approximately 4.3 in 10,000 people in the EU.

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

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

Existing methods

The treatment landscape for patients with DLBCL has evolved substantially since the European Society for Medical Oncology (ESMO) clinical practice guidelines for diagnosis, treatment, and follow-up of DLBCL became publicly available in 2015 (Tilly et al., 2015). However, for patients newly diagnosed with DLBCL, chemoimmunotherapy with an anti-CD20 antibody and an anthracycline-based regimen (often R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) which has a cure rate of approximately 50% (Coiffier 2005) remains the standard for patients who are expected to tolerate such treatment. Patients who have DLBCL that has relapsed or is refractory to systemic therapy may receive salvage therapy with platinum-based immune-chemotherapy regimens such as with rituximab, ifosfamide, carboplatin, etoposide (R-ICE) or rituximab, dexamethasone, high-dose cytarabine, cisplatin (R-DHAP), among others. If an adequate response is achieved, such patients may then receive consolidation with high dose systemic therapy and ASCT. The standard of care chemotherapy used in patients who are ineligible for ASCT includes regimens such as gemcitabine and oxaliplatin (GemOx) ± rituximab or gemcitabine, dexamethasone and cisplatin (GDP) ± rituximab (National Comprehensive Cancer Network, 2021).

According to the ESMO guidelines, there is currently no established standard of care for patients with r/r DLBCL who have been treated with two or more lines of systemic therapies. However, there have been several advancements in the treatment of patients with r/r DLBCL. Several new medicinal products have been approved in the r/r disease setting in the EU after 2015 including polatuzumab (Polivy) in combination with bendamustine and rituximab, tafasitamab (Minjuvi) in combination with lenalidomide, three CAR-T cell therapies [axicabtagene ciloleucel (Yescarta), tisagenlecleucel (Kymriah), and lisocabtagene maraleucel (Breyanzi)], as well as loncastuximab tesirine (Zynlonta). In addition, the bispecific (anti-CD20/CD3) antibody treatments glofitamab (Columvi) and epcoritamab (Tepkinly) have recently received conditional marketing authorisation in the third- and later lines setting.

The sponsor's product odronextamab is intended to treat adults with r/r DLBCL after two or more lines of systemic therapy. An overview of medicinal products authorised for the treatment of relapsed DLBCL in the EU and whether they are considered satisfactory methods of treatment relevant for a discussion on the significant benefit of odronextamab in patients with r/r DLBCL is presented in the table below.

Table 10 Medicinal products authorised for the treatment of 3L+ r/r DLBCL in the EU

Product (INN)	**Procedure #, Approval Date and Type of MA**	**Mechanism of Action (MoA)**	**Therapeutic indication per SmPC**	**Considerations regarding satisfactory methods**
Kymriah (tisagenlecleucel)	EMEA/H/C/004090 22 Aug 2018 Full MA	Anti-CD19 CAR-T	Kymriah is indicated for the treatment of adult patients with r/r DLBCL after two or more lines of systemic therapy	**Satisfactory method**; complete overlap with the proposed therapeutic indication of odronextamab
Yescarta (axicabtagene ciloleucel)	EMEA/H/C/004480 23 Aug 2018 Full MA	Anti-CD19 CAR-T	Yescarta is indicated for the treatment of adult patients with r/r DLBCL and PMBCL, after two or more lines of systemic therapy	**Satisfactory method**; complete overlap with the proposed therapeutic indication of odronextamab
Polivy (polatuzumab vedotin)	EMEA/H/C/004870 16 Jan 2020 Full MA	CD79b ADC	Polivy in combination with bendamustine and rituximab is indicated for the treatment of adult patients with r/r DLBCL who are not candidates for haematopoietic SCT	Not a satisfactory method; does not cover r/r patients who are eligible for haematopoietic SCT, and can be used in second line
Minjuvi (tafasitamab)	EMEA/H/C/005436 26 Aug 2021 CMA	CD19 Monoclonal antibody	Minjuvi is indicated in combination with lenalidomide followed by tafasitamab monotherapy for the treatment of adult patients with r/r DLBCL who are not eligible for ASCT	Not a satisfactory method: the indication is restricted to patient who are not candidates for ASCT and can be used in second line
Breyanzi (lisocabtagene maraleucel)	EMEA/H/C/004731 04 Apr 2022 Full MA	Anti-CD19 CAR-T	Breyanzi is indicated for the treatment of adult patients with r/r DLBCL, PMBCL and FL3B, after two or more lines of systemic therapy	**Satisfactory method**; complete overlap with the proposed therapeutic indication of odronextamab
Zynlonta (loncastuximab tesirine)	EMEA/H/C/005685 20 Dec 2022 CMA	CD19-targeted ADC	Zynlonta as monotherapy is indicated for the treatment of adult patients with r/r DLBCL and HGBL, after two or more lines of systemic therapy	**Satisfactory method**; complete overlap with the proposed therapeutic indication of odronextamab
Columvi (glofitamab)	EMEA/H/C/005751 07 Jul 2023	CD20xCD3 bispecific antibody	Columvi as monotherapy is indicated for the treatment of adult patients with r/r	**Satisfactory method**; complete overlap with the proposed

Product (INN)	Procedure #, Approval Date and Type of MA	Mechanism of Action (MoA)	Therapeutic indication per SmPC	Considerations regarding satisfactory methods
	CMA		DLBCL, after two or more lines of systemic therapy	therapeutic indication of odronextamab
Tepkinly (epcoritamab)	EMEA/H/C/005985 22 Sep 2023 CMA	CD20xCD3 bispecific antibody	Tepkinly as monotherapy is indicated for the treatment of adult patients with r/r DLBCL after two or more lines of systemic therapy	**Satisfactory method**; complete overlap with the proposed therapeutic indication of odronextamab

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

Significant benefit

The sponsor did not seek any protocol assistance from EMA to get advice on a proper approach for collecting the evidence needed to justify significant benefit of odronextamab over existing methods of treatment for patients with r/r DLBCL who have received at least two prior lines of systemic therapy. However, prior to the granting of the orphan designation, the sponsor received scientific advice on the clinical development plan of odronextamab in DLBCL.

Odronextamab is an anti-CD20/CD3 human IgG4-based bispecific antibody therapy, thereby being a T-cell engager that recognizes the T-cell antigen CD3 and the B-cell antigen CD20. The sponsor claimed that odronextamab in monotherapy has demonstrated significant benefit over tisa-cel (Kymriah), axicabtagene ciloleucel (Yescarta), and liso-cel (Breyanzi) based on its robust efficacy in patients with r/r DLBCL who have previously failed the approved CAR-T cell products. The sponsor further claims significant benefit over epcoritamab (Tepkinly) and glofitamab (Columvi) based on a clinically relevant advantage in terms of comparable efficacy but improved safety for r/r DLBCL patients in the third- and later lines setting, and over loncastixumab tesirine (Zynlonta) based on improved efficacy as established with higher response rates for odronextamab despite being studied in a more severe patient population, and a better safety profile.

The claim of significant benefit is based on the results from two open label, multi centre, non-randomised, multi cohort, single-arm studies: Study 1625 (n=127) and study 1333 (n=60). Both studies included adult patients with r/r DLBCL who had received at least two prior lines of systemic therapy, including an anti-CD20 antibody and an alkylating agent. Study 1333 included patients who progressed after prior CAR-T cell therapy.

Study 1625: r/r DLBCL CAR-T cell therapy naïve patients

Study 1625 is an ongoing, open-label, multi-center, multi-cohort, single-arm phase 2 study which is used to obtain the pivotal evidence for odronextamab as monotherapy in patients (≥18 years) with r/r DLBCL who have received at least two prior lines of systemic therapy in the CMA application. Patients with de novo DLBCL or transformed DLBCL, from lower grade neoplasm such as FL or CLL, could be enrolled. The study consisted of 5 disease-specific B-cell NHL cohorts: FL, DLBCL, MCL, MZL, and other B-NHL (containing aggressive B-NHL subtypes not included in the other 4 cohorts). Patients who had received prior treatment with any CAR-T therapy and/or an anti-CD20/CD3 bispecific therapy were excluded from the study. The efficacy data consisted of 127 evaluable patients (defined as patients with or who had the opportunity for response assessment at 12 weeks) from the DLBCL cohort of the study. The DCO date for the updated efficacy and safety analyses provided was 20-Oct-2023. At the DCO, the median duration of study follow-up was 32.5 months (range: 17.4, 36.3) for the DLBCL cohort.

The primary objective of study 1625 is to evaluate the antitumor activity of odronextamab as a single agent as measured by ORR according to the Lugano classification criteria (Cheson et al., 2014) in each of the B-NHL subgroups, including patients with DLBCL who have relapsed after or are refractory to at least two prior lines of systemic therapy, including an anti-CD20 antibody and an alkylating agent. The primary endpoint ORR, which is assessed by an independent central review committee (IRC), is defined as the best overall response (BOR) of a PR or CR which is achieved within 36 weeks after receiving the first dose. Secondary endpoints included DOR, CRR, DOCR, TTR, PFS, and OS.

The median age of the patients in the DLBCL cohort was 67 years (range: 24, 88), and 23.6% (30/127) were ≥75 years of age. Overall, 59.8% (76/127) were men. A similar proportion of DLBCL patients were either white (48.0%; 76/127) or Asian (41.7%; 53/127), and all had a baseline Eastern Cooperative Oncology Group (ECOG) performance status (PS) of either 0 (32.3%; 41/127) or 1

(67.7%; 86/127). The median number of prior lines of anti-lymphoma therapy in the DLBCL cohort was 2 (range: 2-8), and 47.2% (60/127) had received at least 3 prior lines of therapy. Most patients were refractory to any line of therapy (90.6%; 115/127), including 55.1% (70/127) being refractory to first line and 86.6% (110/127) refractory to last line of treatment, 78.0% (99/127) of the patients were refractory to prior anti-CD20 therapy, and 64.6% (82/127) were double refractory to an anti-CD20 antibody and alkylating agent. A total of 17.3% (22/127) had prior ASCT before study entry.

The efficacy results from study 1625 are presented in Table 11 below.

Table 11 Efficacy results in patients with r/r DLBCL in Study 1625

Efficacy endpoints	**Ordspono** **(N=127)**
Objective Response Rate % (n) (95% CI)	52% (66) (43, 61)
Complete response (CR) rate, % (n) (95% CI)	31% (40) (24, 40)
Partial response (PR) rate, % (n) (95% CI)	20% (26) (14, 29)
Duration of Response (DOR)[a]	N=66
Patients with event, % (n)	61% (40)
Median, months (95% CI)	11 (5, 25)
Duration of Complete Response[b]	N=40
Patients with event, % (n)	50% (20)
Median, months (95% CI)	18 (10, NE)

CI=confidence interval; K-M=Kaplan-Meier; NE=Not evaluable. Data Cutoff: 20Oct2023
[a] DOR is defined as the time from the initial occurrence of a documented PR or CR until the patient experiences an event (documented disease progression or death due to any cause, whichever occurs first).
[b] DOCR is defined as the time from the initial occurrence of a documented CR until the patient experiences an event (documented disease progression or death due to any cause, whichever occurs first).

Study 1333: r/r DLBCL patients treated after prior CAR-T cell therapy

Study 1333 was a phase 1, open-label, multi-center, dose-finding and expansion, first-in human (FIH) study of odronextamab monotherapy in patients with CD20+ B-cell malignancies (B-NHL and CLL) previously treated with anti-CD20 antibody therapy with both intravenous (Part A) and subcutaneous (Part B) administration. The antitumor activity and safety of odronextamab was evaluated in patients who were relapsed or refractory to CAR-T cell therapy.

In study 1333, of the 60 r/r DLBCL patients who relapsed or were refractory to CAR-T cell therapy, the median age was 63.0 years (range: 27 to 82), 45.0% were age 65 or older, 65.0% were male, 76.7% were White, 3.3% were Black, 8.3% were Asian, 23.3% with ECOG PS 0, and 76.7% with ECOG PS 1. The median number of systemic prior therapies was 3.0 (range: 2 to 9), and 71.7% were refractory to CAR-T cells for any line of prior therapy. The primary efficacy endpoint was ORR, and the secondary endpoint was DOR as assessed by an IRC using the 2014 Lugano classification criteria (see Table 12).

Table 12. Efficacy results in patients with r/r DLBCL patients after prior CAR-T cell therapy in study 1333

Efficacy endpoints	**Ordspono (N=60)**
Objective Response Rate % (n) (95% CI)	48% (29) (35, 62)
Complete response, % (n) (95% CI))	33% (20) (22, 47)
Partial response, % (n) (95% CI)	15% (9) (7, 27)
Duration of Response (DOR)[a]	N=29
Patients with event, % (n)	34% (10)
Median, months (95% CI)	15 (3, NE)

CI=confidence interval; K-M=Kaplan-Meier; NE=Not evaluable. Data Cutoff: 19Sept2023
[a] DOR is defined as the time from the initial occurrence of a documented PR or CR until the patient experiences an event (documented disease progression or death due to any cause, whichever occurs first).

Significant benefit of odronextamab over the approved CAR-T cell therapies:

In routine clinical practice, it is estimated that approximately 30-70% of patients receiving CAR-T cell therapies will relapse and need subsequent treatment (Pasquini, 2020; Bethge, 2022; Kwon, 2021; Iacoboni, 2021; DiBlasi, 2022). The sponsor argued that for patients who have failed prior CAR-T cell therapies in the r/r setting, odronextamab can serve as an important treatment alternative based on post-CAR-T data from the FIH phase 1 study 1333 which is the only study within the class of anti-CD20/CD3 bispecific antibodies with a dedicated cohort of patients who have r/r DLBCL who have failed prior treatment with a CAR-T cell therapy.

The time required to manufacture CAR-T therapies may preclude their use among patients with rapidly progressing disease. It is estimated that the time between leukapheresis and availability of the manufactured CAR-T cell therapy can range between 19 to 84 days.

Finally, CAR-T cell therapies may not be suitable for all patients with r/r DLBCL due to the increased risk of secondary malignancies (Verdun and Marks, 2023) which requires life-long monitoring. Reports from clinical trials and/or post-marketing AE data sources have recently led to global health authority investigations into the risk of T-cell malignancy with serious outcomes, including hospitalization and death (EMA/PRAC/545005/2023 Jan 2024; FDA Safety and Availability communication 2023).

To demonstrate significant benefit of odronextamab compared to the approved CAR-T cell therapies, selected key baseline clinical characteristics of patients in clinical studies with the CAR-T cell therapies and odronextamab, and a discussion of the study populations, efficacy, and overall safety and tolerability profile of these treatments has been presented below (see Table 13, Table 14, and Table 15).

Table 13 Key characteristics of r/r DLBCL patients in clinical studies with odronextamab and the three approved CAR-T cell therapies

Baseline variables	**Odronextamab**		**Axicabtagene ciloleucel**	**Lisocabtagene maraleucel**	**Tisagenlecleucel**
Study	R1979-HM-1333	R1979-ONC-1625	ZUMA-1	TRANSCEND NHL 001	JULIET
Reference/ Data cut-off	Sep 2023 data cut-off	Oct 2023 data cut-off	Neelapu, 2023 Locke, 2019	Abramson, 2021	Schuster, 2021
N	N=60	N=127	N=101	N=257	N=115
Primary refractory	35 (58.3)	70 (55.1)	26 (25.7)	NR	NR
ECOG 0	14 (23.3)	41 (32.3)	42 (41.6)	69 (26.8)[c]	65 (56.5)
ECOG 1	46 (76.7)	86 (67.7)	59 (58.4)	168 (65.4)[c]	50 (43.5)
ECOG 2	0	0	0[¶]	16 (6.2)[c]	0[¶]
Refractory to last LOT	46 (76.7)	110 (86.6)	78 (77.2)[a]	204 (79.4)	63 (54.8)
# of prior LOTs: 1	0	0	3 (3.0)[j]	9 (3.5)	5 (4.3)
# of prior LOTs: 2	9 (15.0)	67 (52.8)	28 (27.7) [j]	118 (45.9)	51 (44.3)
# of prior LOTs: ≥3	51 (85.0)	60 (47.2)	70 (69.3)	130 (50.6)	59 (51.3)
Prior LOTs, median (range)	3 (2-9)	2 (2-8)	3 (1–10)	3.0 (1-8)	3 (1-6)
Age: Median (range)	63 (27-82)	67 (24-88)	58 (23–76)	63.0 (18-86)	56 (46-64)[f]
Age ≥ 65 years	27 (45.0)	73 (57.5)	24 (23.8)	108 (42.0)	26 (22.6)
IPI risk classification: Low-intermediate (0-2)	25 (41.7)	55 (43.3)	53 (52.5)	150/254 (59.1)	NR
IPI risk classification: High risk (3+)	35 (58.3)	71 (55.9)	48 (47.5)	104/254 (40.9)	84 (73.0)[g] [≥2]
Ann Arbor disease stage I or II	16 (26.7)	23 (18.1)	15 (14.9)	69/254 (27.2)	27 (23.5)
Ann Arbor disease stage III or IV	44 (73.3)	103 (81.1)	86 (85.1)	185/254 (72.8)	88 (76.5)
LDH > ULN	NR	85 (66.9)	85 (84.2)	53 (20.7)	60 (52.2)

Baseline variables	Odronextamab		Axicabtagene ciloleucel	Lisocabtagene maraleucel	Tisagenlecleucel
Prior autologous SCT	NR	22 (17.3)	25 (24.8)	85 (33.1)[e]	56 (48.7)
Bulky disease	24 (40.0)	28 (22.0)	17 (16.8)	29/254 (11.4)[i]	9 (7.8)
DLBCL[h]	60 (100)	127 (100)	93 (92.0)	193 (75.0)	113 (98.3)

Note:
NR: Not reported
a. Refractory to last line is not reported; only refractory to second line or subsequent therapy is reported
b. Only 42 patients with evaluable tumour samples were included
c. ECOG PS at screening
d. Indicates assumption based on eligibility criteria
e. Five patients (2%) received both autologous and allogeneic SCT
f. Inter-quartile range
g. Reported number is for >2 IPI
h. For axicabtagene ciloleucel, lisocabtagene maraleucel, and tisagenlecleucel, the efficacy cohort included patients that may have other forms of NHL that are not categorised as DLBCL
i. Presence of a lesion >10 cm in its longest dimension
j. Including all prior therapies not limited to chemotherapy regimen (Locke 2019)
¶Imputed assuming no missing data

Table 14 Response outcomes to odronextamab and the approved CAR-T cell therapies in clinical studies with r/r DLBCL patients

	Odronextamab		**Axicabtagene ciloleucel**	**Lisocabtagene maraleucel**	**Tisagenlecleucel**
Study	R1979-HM-1333 (post-CAR-T, N=60)	R1979-ONC-1625 (CAR-T naïve, N=127)	ZUMA-1 (N=111)	TRANSCEND (n=298)	JULIET (n=111)
Reference/ Data cut-off	Sep 2023 data cut-off	Oct 2023 data cut-off	Yescarta SmPC 2023	Breyanzi SmPC 2023	Kymriah SmPC 2023
ORR: % (n/N) (95% CI)	48.3% (29/60) (35.2%, 61.6%)	52% (66/127) (42.9%, 60.9%)	All leukapheresed ITT population¶: 66% (56%, 75%) All treated mITT population¶: 72% (62%, 81%)	All leukapheresed patients 60.1% (179/298) (54.2%, 65.7%) Efficacy analysis set 72.7% (157/216) (66.2%, 78.5%)	All enrolled patients: 36.7% (54/147) (28.9%, 45.1%) All infused patients: 54.5% (54/99) (44.2%, 64.6%)
CR rate: % (n/N) (95% CI)	33.3% (20/60) (21.7%, 46.7%)	31.5% (40/127) (23.5%, 40.3%)	All leukapheresed ITT population¶: 47% (95% CI not reported) All treated mITT population¶: 51% (95% CI not reported)	All leukapheresed patients: 43.0% (128/298) (37.3%, 48.8%) Efficacy analysis set: 53.2% (115/216) (46.4%, 60.0%)	All enrolled patients: 27.9% (41/147) (95% CI not reported) All infused patients: 41.4% (41/99) (95% CI not reported)

¶N's not reported in Yescarta SmPC 2023

Table 15 ORR among patients with r/r DLBCL after individual CAR-T therapies in study 1333

	1/20/160 mg (N=20)		0.7/4/20/160 mg (N=40)		Total (N=60)	
	ORR (%)	**95% CI[a]**	**ORR (%)**	**95% CI[a]**	**ORR (%)**	**95% CI[a]**
All DLBCL Post CAR-T Failure Dose Expansion Patients	8/20 (40.0%)	(19.1%, 63.9%)	21/40 (52.5%)	(36.1%, 68.5%)	29/60 (48.3%)	(35.2%, 61.6%)
Prior CAR-T						
Axicabtagene ciloleucel	5/12 (41.7%)	(15.2%, 72.3%)	12/18 (66.7%)	(41.0%, 86.7%)	17/30 (56.7%)	(37.4%, 74.5%)
Lisocabtagene maraleucel	1/1 (100.0%)	(2.5%, 100.0%)	1/5 (20.0%)	(0.5%, 71.6%)	2/6 (33.3%)	(4.3%, 77.7%)
Tisagenlecleucel	0/1 (0.0%)	(0.0%, 97.5%)	2/6 (33.3%)	(4.3%, 77.7%)	2/7 (28.6%)	(3.7%, 71.0%)
Not specified	2/6 (33.3%)	(4.3%, 77.7%)	6/11 (54.5%)	(23.4%, 83.3%)	8/17 (47.1%)	(23.0%, 72.2%)

[a] Clopper-Person exact confidence interval.

Significant benefit of odronextamab over axicabtagene ciloleucel (Yescarta)

The efficacy and safety of axicabtagene ciloleucel in patients with r/r DLBCL, HGBL and PMBCL were evaluated in the pivotal, multicentre, open-label, single-arm phase 1/2 study ZUMA-1 (N=115, intention-to-treat [ITT] population; n=101, modified ITT [mITT] population). The sponsor claimed significant benefit of odronextamab over axicabtagene ciloleucel based on improved efficacy, improved safety, and major contribution to patient care.

The sponsor presented an indirect comparison of the baselines characteristics and results from ZUMA-1 and study 1625. It was noted that patients in the r/r CAR-T naïve DLBCL cohort of study 1625 (N=127) when compared to patients in ZUMA-1 (n=101 mITT) were older (median age: 67 vs. 58 years; proportion of patients ≥65 years: 57.5% vs. 23.8%), had a higher proportion of patients with primary refractory disease (55.1% vs. 25.7%) and IPI risk classification ≥3 (55.9 % vs. 47.5%), respectively. However, median lines of prior therapy and proportion of patients with Ann Arbor disease stage III or IV were higher in ZUMA-1 compared to study 1625.

Acknowledging that differences in study patient characteristics may impact the efficacy outcomes observed across treatments, response outcomes were generally higher for axicabtagene ciloleucel (including in all leukapheresed) compared to odronextamab in the CAR-T naïve cohort of study 1625 (ORR: 66% vs. 52%; CRR: 47% vs. 31.5%).

The sponsor also claimed that the high unmet need among patients who have failed prior CAR-T cell therapy (DiBlasi, 2022) can be addressed by odronextamab based on the compelling efficacy data from study 1333. As of the DCO date of 19-Sep-2023, 60 patients were efficacy evaluable in study 1333 and odronextamab demonstrated clinically meaningful ORR and CRR (Table 11) with a median DOR of 14.8 months (95% CI: 2.8, NE) (Table 11). Study 1333 included 30 patients who had failed axicabtagene ciloleucel prior to receiving odronextamab and the ORR in this subset of patients was 56.7% (17/30; 95% CI: 37.4, 74.5) (Table 11), which was comparable to the ORR of 52% from the CAR-T naïve r/r DLBCL cohort in study 1625.

Although the time between leukapheresis and availability of the manufactured axicabtagene ciloleucel is expected to range between 3 to 4 weeks, a recent meta-analysis estimated the median time between leukapheresis and axicabtagene ciloleucel infusion to be 31 days (range: 27 to 62 days) (Jacobson, 2023) which may preclude its use among patients with high-risk features, for example bulky disease, which are associated with poor outcomes and rapidly progressing disease. In contrast, odronextamab is a readily available off-the-shelf treatment option that can be available for patients without any delays.

Additionally, the sponsor claimed that odronextamab has lower rates of grade ≥3 CRS and neurotoxicity compared to axicabtagene ciloleucel and has a manageable safety profile related to other serious events. Any grade of CRS was observed to occur in 51.7% (61/118) of patients treated with odronextamab compared to 93% (100/108) with axicabtagene ciloleucel (EMA, Yescarta EPAR, 2018), and grade ≥3 was 0.8% (1/118) versus 12% (13/108), respectively. Neurotoxicity of any grade was reported to 39.3% versus 66% (71/108), and grade ≥3 was 7.3% (16/219) versus 31% (34/108) for odronextamab and axicabtagene ciloleucel, respectively. AEs of infection of any grade was 58.4% (128/219) versus 40% (43/108), and for grade ≥3 was 34.7% (76/219) versus 27% (29/108) for odronextamab and axicabtagene ciloleucel, respectively.

COMP discussion

The efficacy analysis in the subset of patients with prior CAR-T cell therapy in the DLBCL cohort of study 1333 showed that odronextamab offered a clinically meaningful benefit for those patients who have progressed or relapsed after prior treatment with axicabtagene ciloleucel, as they achieved high and sustained ORR to odronextamab. The responses observed in this subgroup of patients is considered to constitute a clinically relevant advantage for patients with r/r DLBCL in the third- and later lines setting.

The claim of improved safety based on the frequencies of overlapping toxicities does not reflect the whole picture and biases due to differences in patient characteristic cannot be excluded. Given the limited experience with odronextamab from a small single-arm study with limited follow-up, the claim of a better safety profile in comparison to axicabtagene ciloleucel cannot be concluded on at present stage and no adequate quantification is possible for the descriptive cross-study comparisons presented.

The sponsor finally argued that the time between leukapheresis and CAR-T cell infusion (49 days, Jacobson, 2023) which may preclude the use of CAR-T treatments among patients with rapidly progressing disease. According to the sponsor, odronextamab offers a significant benefit to patients with r/r DLBCL by being readily available when needed. However, no data was submitted to support such a claim.

In conclusion, the claim of significant benefit of odronextamab compared to axicabtagene ciloleucel (Yescarta) for adult patients with r/r DLBCL in the third- and later lines setting can be considered established based on the data provided.

Significant benefit of odronextamab over lisocabtagene maraleucel (Breyanzi)

The efficacy and safety of lisocabtagene maraleucel in patients with r/r DLBCL, HGBL, PMBCL, and FL grade 3b who had received at least two lines of prior therapy were evaluated in the pivotal, global, multicentre, open-label, single-arm phase 1 study TRANSCEND (N=298, ITT; n=257, mITT). The sponsor claimed significant benefit of odronextamab over lisocabtagene maraleucel based on improved efficacy, improved safety, and major contribution to patient care.

The ponsor presented an indirect comparison of the baselines characteristics and results from TRANSCEND and study 1625. It was noted that patients in TRANSCEND were younger compared to patients in the r/r DLBCL CAR-T naive cohort of study 1625 (median age: 63 vs. 67, proportion of patients ≥65 years: 42% vs. 57.5%), and less severe based on high-risk features including refractory to last line of therapy (79.4% vs. 86.6%), IPI risk classification 3+ (40.9% vs. 55.9%), Ann Arbor disease stage III/IV (72.8% vs. 81.1%), and bulky disease (11.4% vs. 22.0%).

Acknowledging that differences in study patient characteristics may impact the efficacy outcomes observed across treatments, response outcomes were generally higher for lisocabtagene maraleucel (including in all leukapheresed) compared to odronextamab in the CAR-T naïve cohort of study 1625 (ORR: 60.1% vs. 52%; CRR: 43.0% vs. 31.5%).

The sponsor also claimed that the high unmet need among patients who have failed prior treatment with CAR-T cell therapy (DiBlasi, 2022) can be addressed by odronextamab based on the compelling efficacy observed in study 1333 (Table 11) with a median DOR of 14.8 months (Table 11). There were limited number of patients in study 1333 who had failed lisocabtagene maraleucel (n=6) prior to receiving odronextamab resulting in high variability in the response outcome in this subgroup of patients (ORR: 33.3% [2/6]; 95% CI: 4.3, 77.7). In study 1333, most patients with a CAR-T cell therapy that had an identifiable medicine name prior to odronextamab initiation had received axicabtagene ciloleucel (n=30). However, since lisocabtagene maraleucel and axicabtagene ciloleucel target the same CD19 antigen, despite using different costimulatory endodomain, derived from the 4-1BB molecule (CD137) for lisocabtagene maraleucel and CD28 for axicabtagene ciloleucel, there is lack of scientific rationale suggesting that efficacy of odronextamab would differ by type of prior CD19-directed CAR-T cell therapy. Hence, the sponsor argued that significant benefit of odronextamab after lisocabtagene maraleucel failure can be extrapolated from efficacy data from the subset of patients from study 1333 who had failed prior treatment with axicabtagene ciloleucel.

It is estimated that the time between leukapheresis and availability of the manufactured lisocabtagene maraleucel can range between 19 to 84 days (EMA, Breyanzi EPAR, 2023) thereby precluding its use among patients with rapidly progressing disease. In contrast, odronextamab is a readily available off-the-shelf treatment option that can be available for patients without any delays.

The sponsor also claimed that odronextamab has a favourable safety profile compared to lisocabtagene maraleucel with lower rates of grade ≥3 CRS (0.8% vs. 2.2%) and grade ≥3 neurotoxicity (7.3% vs. 9.7%). Although AEs of serious infections were higher for odronextamab compared to lisocabtagene maraleucel (32.9% [72/219] vs. 10.4%), it was noted that the risk of infection is adequately managed by risk mitigation guidance.

COMP discussion

The sustained ORR observed in the relatively large number of patients treated with odronextamab who had earlier received treatment with axicabtagene ciloleucel in the DLBCL cohort of study 1333 can be extrapolated to patients who have failed previous treatment with lisocabtagene maraleucel.

Given the limited experience with odronextamab from a small single-arm study with limited follow-up, the claim of improved safety in comparison to lisocabtagene maraleucel cannot be concluded on at present stage and no adequate quantification is possible for the descriptive cross-study comparison presented.

The sponsor finally argued that the time between leukapheresis and CAR-T cell infusion (49 days, Jacobson, 2023) which may preclude the use of CAR-T treatments among patients with rapidly progressing disease. According to the sponsor, odronextamab offers a significant benefit to patients

with r/r DLBCL by being readily available when needed. However, no data was submitted to support such a claim.

In conclusion, the significant benefit of odronextamab over lisocabtagene maraleucel (Breyanzi) can be considered justified based on a clinically relevant advantage for adult patients with r/r DLBCL who have progressed or relapsed after previous treatment with the authorised CD19-directed CAR-T cell products in the third- and later lines setting.

Significant benefit of odronextamab over tisagenlecleucel (Kymriah)

The efficacy and safety of tisagenlecleucel in patients with r/r DLBCL who had received two or more lines of therapy were evaluated in the pivotal, global, multicentre, open-label, single-arm phase 2 study C2201, also known as JULIET (N=167, ITT; n=115, mITT). The sponsor claimed significant benefit of odronextamab over tisagenlecleucel based on improved efficacy, improved safety, and major contribution to patient care.

An indirect comparison of the baselines characteristics and results from JULIET and study 1625 was presented. The sponsor noted that patients in JULIET were younger compared to patients in the r/r DLBCL cohort of study 1625 [median age: 56 vs. 67; proportion of patients ≥65 years: 22.6% vs. 57.5%), and less severe based on high-risk features including refractory to last line of therapy (54.8% vs. 86.6%), Ann Arbor disease stage III/IV (76.5% vs. 81.1%), and bulky disease (7.8% vs. 22.0%). In general, the patient population in JULIET had a lower proportion of patients with high-risk features, similar ORR, but numerically higher CRR compared to the CAR-T naïve r/r DLBCL cohort of odronextamab in study 1625 (all infused: ORR 54.5% vs. 52%; CRR 41.4% vs. 31.5%, respectively) (Kymriah SmPC, 2023).

The sponsor also claimed that the high unmet need among patients who have failed prior treatment with CAR-T cell therapy (DiBlasi, 2022) can be addressed by odronextamab based on the compelling efficacy observed in study 1333 (Table 11) with a median DOR of 14.8 months (Table 11). There were limited number of patients in study 1333 who had failed tisagenlecleucel (n=7) prior to receiving odronextamab resulting in high variability in the response outcome in this subgroup of patients (ORR: 28.6% [2/7]; 95% CI: 3.7, 71.0). In study 1333, most patients with a CAR-T cell therapy that had an identifiable medicine name prior to odronextamab initiation had received axicabtagene ciloleucel (n=30). However, all approved CAR-T cell therapies including tisagenlecleucel target the same CD19 antigen, although they differ somewhat according to their costimulatory endodomain, derived from CD28 for axicabtagene ciloleucel and the 4-1BB molecule (CD137) for lisocabtagene maraleucel and tisangenlecleucel. The sponsor emphasised that given the lack of scientific rationale suggesting that efficacy of odronextamab would differ by type of prior CD19-directed CAR-T therapy, the significant benefit of odronextamab after tisagenlecleucel failure can be extrapolated from efficacy data from the subset of patients from study 1333 who had failed prior treatment with axicabtagene ciloleucel.

Although the time between leukapheresis and availability of the manufactured tisagenlecleucel therapy can range between 3 to 4 weeks, a recent meta-analysis estimated the median time between leukapheresis and tisagenlecleucel infusion to be 49 days (range: 32 to 64 days) (Jacobson, 2023) which may preclude its use among patients with rapidly progressing disease. In contrast, odronextamab is a readily available off-the-shelf treatment option that can be available for patients without any delays.

It was also argued that odronextamab has a favourable safety profile compared to tisagenlecleucel with lower rates of grade ≥3 CRS (0.8% [1/118] vs. 23.2%) and grade 3/4 neurotoxicity events (7.3% [16/219] vs. 12.1%). Although AEs of serious infections were higher for odronextamab compared to

tisagenlecleucel (32.9% [72/219] vs. 14.1%), the risk of infection is adequately managed by risk mitigation guidance.

COMP discussion

It is agreed that the sustained ORR observed in the relatively large number of patients treated with odronextamab who had earlier received treatment with axicabtagene ciloleucel in the DLBCL cohort of study 1333 can be extrapolated to patients who have failed previous treatment with tisagenlecleucel.

The sponsor finally argued that the time between leukapheresis and CAR-T cell infusion (49 days, Jacobson, 2023) which may preclude the use of CAR-T treatments among patients with rapidly progressing disease. According to the sponsor, odronextamab offers a significant benefit to patients with r/r DLBCL by being readily available when needed. However, no data was submitted to support such a claim.

The claim of improved safety based on the frequencies of overlapping toxicities does not reflect the whole picture and biases due to differences in patient characteristic cannot be excluded. Given the limited experience with odronextamab from a small single-arm study with limited follow-up, the claim of a better safety profile in comparison to tisagenlecleucel cannot be concluded on at present stage and no adequate quantification is possible for the descriptive cross-study comparisons presented.

In conclusion, the claim of significant benefit of odronextamab compared to tisagenlecleucel (Kymriah) can be considered justified based on a clinically relevant advantage for adult patients with r/r DLBCL who have progressed or relapsed after previous treatment with the authorised CD19-directed CAR-T cell products in the third- and later lines setting.

Significant benefit of odronextamab over anti-CD20 X CD3 bispecific antibodies:

Summaries of selected key baseline characteristics of patients in clinical studies with odronextamab and the two conditionally approved anti-CD20/CD3 bispecific antibodies Columvi (glofitamab) and Tepkinly (epcoritamab) in r/r DLBCL have been presented in Table 16.

Table 16 Key characteristics of r/r DLBCL patients in clinical studies with odronextamab, glofitamab, and epcoritamab

Baseline variables	Odronextamab		Glofitamab	Epcoritamab
Study	R1979-HM-1333	R1979-ONC-1625	NP30179	GCT3013-01
Reference/ Data cut-off	Sep 2023 data cut-off	Oct 2023 data cut-off	Dickinson, 2022; EMA, Columvi EPAR 2022	Thiemblemont, 2022; Tepkinly SmPC 2023; EMA, Tepkinly EPAR 2022
N	N=60	N=127	N=155 (1pt untreated n=154)	DLBCL N=139
Primary refractory	35 (58.3)	70 (55.1)	90/154 (58.4)	82 (59.0)
ECOG 0	14 (23.3)	41 (32.3)	69 (44.8)[a]	67 (48.2)
ECOG 1	46 (76.6)	86 (67.7)	84 (54.5)[a]	67 (48.2)
ECOG 2	0	0	1 (0.6)[a]	5 (3.6)
Refractory to last LOT	46 (76.7)	110 (86.6)	131 (84.5)	114 (82.0)
# of prior LOTs: 1	0	0	0	0
# of prior LOTs: 2	9 (15.0)	67 (52.8)	61 (39.4)	41 (29.5)
# of prior LOTs: ≥3	51 (85.0)	60 (47.2)	94 (60.1)	98 (70.1)
Prior LOTs, median (range)	4 (2-9)	2 (2-8)	3 (2–7)	3 (2–11)
Age: Median (range)	63 (27-82)	67 (24-88)	66 (21–90)	66 (22–83)
Age ≥ 65 years	21 (47.7)	73 (57.5)	84 (54.2)	73 (52.5)
IPI risk classification: Low-intermediate (0-2)	25 (41.7)	55 (43.3)	74 (37.7)	55/137 (40.1)[b]
IPI risk classification: High risk (3+)	35 (58.4)	71 (55.9)	81 (52.3)	82/137 (59.9)[b]
Ann Arbor disease stage I or II	16 (26.7)	23 (18.1)	35/151 (23.2)[c]	35 (25.2)
Ann Arbor disease stage III or IV	44 (73.3)	103 (81.1)	116/151 (76.8)[c]	104 (74.8)
Bulky disease	24 (40.0)	28 (22.0)	64/154 (41.6)[d] 19/154 (12.3)[e]	NR
Transformed DLBCL (Richter)	NR	7 (5.5)	NR	NR
Prior CAR-T therapy	60 (100%)	0 (0)	52 (33.5)	53 (38.1)

NR: Not reported
a. ECOG PS is unknown for 1 pt
b. Imputed assuming no missing data
c. Stage data unknown for 4 patients (of 155)
d. Bulky disease >6cm
e. Bulky disease >10cm

Significant benefit of odronextamab over glofitamab (Columvi)

The efficacy and safety of glofitamab in adult patients with r/r DLBCL and HGBL after two or more lines of systemic therapy, including an anti-CD20 monoclonal antibody and an anthracycline agent, were

evaluated in the pivotal, global, multicentre, multi-cohort, open-label, single-arm phase 1/2 study NP30179 (N=155) (Dickinson et al., 2022). The sponsor claimed significant benefit of odronextamab over glofitamab based on improved efficacy and improved safety.

As presented in Table 15, the study populations were generally similar but patients in study 1625 with odronextamab had a slightly higher proportion of patients with Ann Arbor III/IV (81.1% vs. 76.8%) and IPI 3+ (55.9% vs. 52.3%) compared to study NP30179 with glofitamab. In addition, patients with transformed DLBCL (Richter), which is associated with poor prognosis, were not eligible in study NP30179, whereas 5.5% of patients in study 1625 had Richter transformation. On the other hand, DLBCL patients in study NP30179 were slightly more pretreated compared to those included in the DLBCL cohort of study 1625. Study NP30179 with glofitamab also included a subgroup of patients with prior CAR-T exposure (33.5% [52/155]), whereas odronextamab was studied in two separate studies, study 1333 which included a dedicated cohort of DLBCL patients with prior CAR-T cell therapy failure and study 1625 among CAR-T naïve patients.

Response outcomes observed in the respective clinical studies, including those in CAR-T cell naive subgroups and in the post-CAR-T setting are presented in Table 17. Patients receiving glofitamab and odronextamab had similar responses in all DLBCL populations analysed.

Table 17. Response outcomes to odronextamab and glofitamab in clinical studies with r/r DLBCL patients

	Odronextamab		**Glofitamab**
Study	R1979-HM-1333 (post-CAR-T, N=60)	R1979-ONC-1625 (CAR-T naïve, N=127)	NP30179
Reference/ Data cut-off	Sep 2023 data cut-off	Oct 2023 data cut-off	Columvi SmPC 2024 Columvi Orphan assessment report 2023
Efficacy outcomes			
ORR: % (n/N) (95% CI)	48.3% (29/60) (35.2%, 61.6%)	52% (66/127) (42.9%, 60.9%)	Overall ITT (n=108): 50% (54/108) (40.2%, 59.8%) CAR-T naive subgroup: 52.4% (95% CI not reported) CAR-T failure subgroup: 50.0% (95% CI not reported)
CR rate: % (n/N) (95% CI)	33.3% (20/60) (21.7%, 46.7%)	31.5% (40/127) (23.5%, 40.3%)	Overall ITT: 35.2% (38/108) (26.2%, 44.9%) CAR-T naive subgroup: 41.7% (95% CI not reported) CAR-T failure subgroup: 35.2% (95% CI not reported)

The sponsor argued that odronextamab has demonstrated significant benefit over glofitamab based on clinically meaningful responses with odronextamab observed across patient subgroups with all levels of CD20 expression, including CD20 low and no detectable CD20 expression. Limited data were available on patients with CD20-negative disease treated with glofitamab. In study NP30179, all 3 patients with

CD20-negative disease had progressive disease as their best response to glofitamab and died during follow-up. Based on these data, it was unclear whether recent anti-CD20 treatment negatively impacts glofitamab activity, and a warning was included in its approved SmPC that use in patients with CD20-negative DLBCL may have less benefit compared to patients with CD20-positive DLBCL and that the potential risks and benefits associated with treatment of patients with CD20-negative DLBCL with Columvi should be considered.

In contrast, among patients receiving odronextamab in study 1625 and having very low or no detectable CD20 expression (n=7), a subgroup analysis conducted by the sponsor demonstrated that 71.4% (5/7) of these patients were able to achieve a CR (including 3 patients with disease with no detectable CD20 expression).

Another aspect of significant benefit of odronextamab over glofitamab comes from the safety profile related to CRS. Low and high-grade CRS events reported with glofitamab were more commonly reported (any grade: 67.6%, grade 3: 2.8%, and grade 4: 1.4%) (Columvi SmPC, 2024). The safety and tolerability of odronextamab demonstrates that odronextamab has a favourable CRS related safety profile (CRS grade ≥3: 0.8% [1/118], no grade 4 or 5 CRS) compared to glofitamab. Although the risk of serious infection is higher for odronextamab than for glofitamab (32.9% [72/219] vs. 18.2% [28/152], respectively), it is adequately managed by risk mitigation guidance.

COMP discussion

The sponsor claimed improved efficacy based on clinically meaningful responses in patients with CD20 low or CD20-negative disease and improved safety in the entire target population.

Regarding the argument on improved efficacy in patients with CD20 low or CD20-negative disease the COMP considered that the data are too limited to justify this argument. The specific claim would rely on post-hoc subgroup analysis with limited number of samples and is not found appropriate. Of the 122 patients with DLBCL with local CD20 assessment available in the clinical database (out of a total of 127 patients [96%]), 10 patients were reported not to have CD20 expression. Of these, 2 achieved a CR, 1 a PR, 3 had PD, and 4 were not evaluable. However, these data are not considered sufficient to establish significant benefit of odronextamab over glofitamab in r/r DLBCL.

Based on the mechanism of action of odronextamab, a response from an anti-CD20 therapy is not to be expected in a tumour that is completely and homogenously negative for the target antigen (CD20).

It is well-known that assessment of CD20 expression may be challenging due to lack of sufficient and/or representative tumour material and dependent on the technical approaches, often IHC or flow cytometry. No companion diagnostic is required to assess CD20 expression prior to use of odronextamab. Thus, a benefit is assumed in a population where this effect has not been assessed.

Given the limited experience with odronextamab from a small single-arm study with limited follow-up, the claim of improved safety in comparison to glofitamab cannot be concluded on at present stage and no adequate quantification is possible for the descriptive cross-study comparison presented.

In conclusion, the claim of significant benefit of odronextamab compared to glofitamab (Columvi) for adult patients with r/r DLBCL in the third- and later lines setting cannot be considered established based on the data provided.

Significant benefit of odronextamab over epcoritamab (Tepkinly)

The efficacy and safety of epcoritamab were evaluated in the pivotal, global, multicentre, multi-cohort, open-label, single-arm phase 1/2 study GCT3013-01 in patients with r/r NHL, including DLBCL, after two or more lines of systemic therapy (Thieblemont et al., 2022). The pivotal aggressive NHL cohort

consisted of 139 patients with DLBCL (Jurczak et al., 2023). The sponsor claimed significant benefit of odronextamab over epcoritamab based on improved efficacy and improved safety.

For epcoritamab, patients had a median age of 66 years, 52.5% (73/139) of patients were ≥ 65 years of age, 59.9% (82/137) had IPI risk classification 3+, 74.8% (104/139) had Ann Arbor disease stage III or IV, 82.0% (114/139) were refractory to last line of therapy, the median number of prior lines of therapy was 3 (range: 2–11). Study GCT3013-01 with epcoritamab included a subgroup of patients with prior CAR-T exposure (38.1% [53/139]) whereas odronextamab was studied in two separate studies, study 1333 which included a dedicated cohort of patients who had failed prior CAR-T cell therapy and study 1625 among CAR-T naïve patients.

The sponsor noted that the patient populations were generally similar between the two treatments, but that a higher percentage of patients treated with odronextamab in study 1625 compared to those treated with epcoritamab in study GCT3013-01 had high-risk features including Ann Arbor disease stage III or IV (81.1% vs. 74.8%), and were refractory to last line of therapy (86.6% vs. 82.0%). In contrary, a higher proportion of DLBCL patients in study GCT3013-01 had primary refractory disease (59.0% vs. 55.1%) and were slightly more pretreated (median lines of prior therapy: 3 [range: 2–11] vs. 2 [range: 2-8]) compared to those included in the DLBCL cohort of study 1625. Study GCT3013-01 with epcoritamab also included a subgroup of patients with prior CAR-T exposure (38.1% [53/139]) whereas odronextamab was studied in two separate studies, study 1333 which included a dedicated cohort of patients with prior CAR-T cell therapy failure and study 1625 among CAR-T naïve patients.

Response outcomes observed in the respective clinical studies, including those in CAR-T cell naive subgroups and in the post-CAR-T setting are presented in Table 17. Patients receiving odronextamab had numerically lower responses compared to those treated with epcoritamab in all DLBCL populations analysed.

Table 18. Response outcomes to odronextamab and epcoritamab in clinical studies with r/r DLBCL patients

	Odronextamab		**Epcoritamab**
Study	R1979-HM-1333 (post-CAR-T, N=60)	R1979-ONC-1625 (CAR-T naïve, N=127)	GCT3013-01
Reference/ Data cut-off	Sep 2023 data cut-off	Oct 2023 data cut-off	Tepkinly SmPC 2024 Tepkinly EMA Orphan assessment report 2023
Efficacy outcomes			
ORR: % (n/N) (95% CI)	48.3% (29/60) (35.2%, 61.6%)	52% (66/127) (42.9%, 60.9%)	Overall ITT (n=139): 62% (86/139) (53.3%, 70%) CAR-T naive subgroup (n=86): 67.4% (58/86) (95% CI not reported) CAR-T failure subgroup (n=53): 52.8% (38.6%, 66.7%)
CR rate: % (n/N) (95% CI)	33.3% (20/60) (21.7%, 46.7%)	31.5% (40/127) (23.5%, 40.3%)	Overall ITT (n=139): 39% (54/139) (30.7%, 47.5%) CAR-T naive subgroup (n=86): 41.9% (36/86) (95% CI not reported) CAR-T failure subgroup (n=53): 35.8% (23.1%, 50.6%)

The sponsor argued that odronextamab has demonstrated significant benefit over epcoritamab based on clinically meaningful responses with odronextamab observed across patient subgroups with all levels of CD20 expression, including patients with CD20 low and CD20-negative disease. Limited data were available on patients with CD20-negative DLBCL treated with epcoritamab (Tepkinly). Of the 157 patients in study GCT3013-01, 8 patients (5.1%) were CD20-negative (level of expression of CD20<50%) and all but one of these patients did not respond to treatment (EMA, 2023 Tepkinly EPAR). It is important to note that the responding patient had a CD20 expression level of approximately 20%. Based on these data, it was unclear whether recent anti-CD20 treatment negatively impacts epcoritamab activity, and a warning was included in its approved SmPC that use in patients with CD20-negative DLBCL may have less benefit compared to patients with CD20-positive DLBCL and that the potential risks and benefits associated with treatment of patients with CD20-negative DLBCL with Tepkinly should be considered.

In contrast, among patients receiving odronextamab in study 1625 and having very low or no detectable CD20 expression (n=7), a subgroup analysis conducted by the sponsor demonstrated that 71.4% (5/7) of these patients were able to achieve a CR (including 3 patients with disease with no detectable CD20 expression).

Finally, the sponsor argued that odronextamab provides a significant benefit over epcoritamab based on an improved safety profile as demonstrated by the lower rates of CRS grade ≥3 and no immune effector cell-associated neurotoxicity syndrome (ICANS). AE of CRS grade 1/2 for patients receiving epcoritamab was 49.3% (73/148) and grade ≥3 was 2.7% (4/148). ICANS (all grade) occurred in 6.1% (9/148) of patients with DLBCL in study GCT3013-01, 5.4% experienced ICANS grade 1 or 2 and one patient (0.7% [1/148]) experienced a fatal ICANS event (EMA, Tepkinly EPAR, 2023). Although the risk of serious infection is higher for odronextamab compared to epcoritamab (32.9% vs. 16.2%, respectively), it is adequately managed by risk mitigation guidance.

In summary, odronextamab's significant benefit over epcoritamab is based on an improved safety profile as demonstrated by the lower rates of grade 3 and above CRS and no ICANS. This significant benefit is further supported by the clinically meaningful responses observed with odronextamab among patients with CD20 low or CD20-negative disease. Given the impact of all these factors on patients' health, these factors demonstrate significant benefit of odronextamab over epcoritamab in the treatment of patients with r/r DLBCL.

COMP discussion

The sponsor claimed improved efficacy based on clinically meaningful responses in patients with CD20 low or CD20-negative disease and improved safety in the entire target population.

Regarding the argument on improved efficacy in patients with CD20 low or CD20-negative disease the COMP considered that the data are too limited to justify this argument. The specific claim would rely on post-hoc subgroup analysis with limited number of samples and is not found appropriate. Of the 122 patients with DLBCL with local CD20 assessment available in the clinical database (out of a total of 127 patients [96%]), 10 patients were reported not to have CD20 expression. Of these, 2 achieved a CR, 1 a PR, 3 had PD, and 4 were not evaluable. However, these data are not considered sufficient to establish significant benefit of odronextamab over epcoritamab in r/r DLBCL.

Based on the mechanism of action of odronextamab, a response from an anti-CD20 therapy is not to be expected in a tumour that is completely and homogenously negative for the target antigen (CD20).

It is well-known that assessment of CD20 expression may be challenging due to lack of sufficient and/or representative tumour material and dependent on the technical approaches, often IHC or flow cytometry. No companion diagnostic is required to assess CD20 expression prior to use of odronextamab. Thus, a benefit is assumed in a population where this effect has not been assessed.

Given the limited experience with odronextamab from a small single-arm study with limited follow-up, the claim of improved safety in comparison to epcoritamab cannot be concluded on at present stage and no adequate quantification is possible for the descriptive cross-study comparison presented.

In conclusion, the claim of significant benefit of odronextamab compared to epcoritamab (Tepkinly) for adult patients with r/r DLBCL in the third- and later lines setting cannot be considered established based on the data provided.

Significant benefit of odronextamab over loncastuximab tesirine (Zynlonta)

The efficacy and safety of the CD19-directed monoclonal antibody loncastuximab tesirine in adult patients with r/r DLBCL and HGBL after at least two prior systemic regimens were evaluated in the pivotal, global, multicentre, open-label, single-arm phase 2 study LOTIS-2 (N=145). The sponsor claimed significant benefit of odronextamab over loncastuximab tesirine based on improved efficacy and improved safety.

An indirect comparison of the baselines characteristics and results from LOTIS-2 and study 1625 was presented. Summaries of selected key baseline characteristics of patients with r/r DLBCL in the registrational studies for odronextamab and loncastuximab tesirine have been presented in Table 19.

Table 19 Key characteristics of r/r DLBCL patients in clinical studies with odronextamab and loncastuximab tesirine (Zynlonta)

Baseline variables	**Odronextamab**		**Loncastuximab tesirine**
Study	R1979-HM-1333	R1979-ONC-1625	LOTIS-2
Reference/ Data cut-off	Sep 2023 data cut-off	Oct 2023 data cut-off	Caimi, 2021 Caimi, 2023 EMA, Zynlonta EPAR 2022
N	N=60	N=127	N=145(DLBCL: n=128)
Primary refractory	35 (58.3)	70 (55.1)	29 (20)
ECOG 0	14 (23.3)	41 (32.3)	58 (40.0)
ECOG 1	46 (76.6)	86 (67.7)	78 (53.8)
ECOG 2	0	0	9 (6.2)
Refractory to last LoT	46 (76.7)	110 (86.6)	89 (61.4)
# of prior LOTs: 1	0	0	0
# of prior LOTs: 2	9 (15.0)	67 (52.8)	63 (43.4)
# of prior LOTs: ≥3	51 (85.0)	60 (47.2)	82 (56.6)
Prior LOTs, median (range)	4 (2-9)	2 (2-8)	3 (2–7)
Age: Median (range)	63 (27-82)	67 (24-88)	66 (23–94)
Age ≥65 years old	21 (47.7)	73 (57.5)	80 (55.2)
IPI risk classification: Low-intermediate risk (0-2)	25 (41.7)	55 (43.3)	57.2%
IPI risk classification: High risk (3+)	35 (58.4)	71 (55.9)	43.8%[a]
Ann Arbor disease stage I or II	16 (26.7)	23 (18.1)	33 (22.8)
Ann Arbor disease stage III or IV	44 (73.3)	103 (81.1)	112 (77.2)
Bulky disease	24 (40.0)	28 (22.0)	8 (5.5)[b]
Prior CAR-T therapy	60 (100%)	0 (0)	14 (9.7)

Notes: a - Imputed proportion assuming with no missing data and actual number of patients cannot be calculated as denominator is not reported
b - Bulky disease defined as >=10cm

In LOTIS-2, there were no study inclusion criteria with regards to prior use of an anti-CD20 antibody or alkylating agent and patients with bulky disease were expected to be excluded from the study based on study eligibility criteria. Additionally, post-CAR-T data from LOTIS-2 was limited to a subgroup of patients with prior CAR-T exposure (9.7%; 14/145) whereas odronextamab had two separate studies as discussed above. Since LOTIS-2 had a low proportion of patients with prior CAR-T exposure (n=14), the efficacy of loncastuximab tesirine is not well characterized in this patient population.

Several differences were noted in the baseline and clinical characteristics of patients in LOTIS-2 and the CAR-T naïve patient population in study 1625 of odronextamab. Overall, patients in the LOTIS-2 were less severe based on high-risk features including primary refractory (20% vs. 55.1%), refractory

to last line of therapy (61.4%vs. 86.6%), and bulky disease (5.5% vs. 22.0%) compared to patients in the DLBCL cohort of study 1625. On the other hand, DLBCL patients in LOTIS-2 were slightly more pretreated compared to those included in the DLBCL cohort of study 1625.

The sponsor emphasised that despite being evaluated in a more severe study population, response outcomes were higher for patients receiving odronextamab compared to loncastuximab tesirine in both CAR-T naïve and post-CAR-T r/r DLBCL populations as shown in Table 20.

Table 20. Response outcomes to odronextamab and loncastuximab tesirine in clinical studies with r/r DLBCL patients

	Odronextamab		**Loncastuximab tesirine**
Study	R1979-HM-1333 (post-CAR-T, N=60)	R1979-ONC-1625 (CAR-T naïve, N=127)	LOTIS-2 (N=145)
Reference/ Data cut-off	Sep 2023 data cut-off	Oct 2023 data cut-off	Zynlonta SmPC, 2023 Zynlonta Orphan Assessment report, 2022
Efficacy outcomes			
ORR: % (n/N) (95% CI)	48.3% (29/60) (35.2%, 61.6%)	52% (66/127) (42.9%, 60.9%)	Overall ITT: 48.3% (39.9%, 56.7%) CAR-T exposed subgroup (n=14) 42.9% (6/14) (95% CI not reported)
CR rate: % (n/N) (95% CI)	33.3% (20/60) (21.7%, 46.7%)	31.5% (40/127) (23.5%, 40.3%)	Overall ITT: 24.8% (18.0%, 32.7%) CAR-T exposed subgroup (n=14) 21.4% (3/14) (95% CI not reported)

Given its mode of action, serious events such as effusion, oedema, myelosuppression, infections and photosensitivity and cutaneous reactions have been reported with loncastuximab tesirine. TEAEs of high-grade neutropenia (grade ≥3: 26%) and thrombocytopenia (grade ≥3: 18%) were also reported for loncastuximab tesirine (Zynlonta SmPC, 2023).

The safety and tolerability of odronextamab demonstrates that the identified risks of odronextamab are CRS and serious infections, which can be adequately managed by risk mitigation guidance. Overall, odronextamab has a manageable safety profile and lower rates of high-grade neutropenia (grade ≥3: 16.9% [37/219]) and thrombocytopenia (grade ≥3: 8.2% [18/219]) compared to loncastuximab tesirine.

In summary, odronextamab's significant benefit over loncastuximab tesirine is based on the favourable efficacy in the CAR-T naïve and post-CAR-T setting as well as lower rates of high-grade neutropenia and thrombocytopenia.

COMP discussion

The sponsor claimed significant benefit of odronextamab over loncastuximab tesirine based on improved efficacy and improved safety.

The data presented are not considered sufficient to establish significant benefit in terms of improved efficacy of odronextamab over loncastuximab tesirine in r/r DLBCL patients. In addition, the claim of improved safety based on the frequencies of overlapping toxicities does not reflect the whole picture and biases due to differences in patient characteristic cannot be excluded. Given the limited experience with odronextamab from a small single-arm study with limited follow-up, the claim of a better safety profile in comparison to loncastuximab tesirine cannot be concluded on at present stage and no adequate quantification is possible for the descriptive cross-study comparisons presented.

In conclusion, the claim of significant benefit of odronextamab compared to loncastuximab tesirine for adult patients with r/r DLBCL in the third- and later lines setting cannot be considered established based on the data provided.

Overall COMP conclusions

The claim of significant benefit based on a clinically relevant advantage for odronextamab (Ordspono) over axicabtagene ciloleucel (Yescarta), lisocabtagene maraleucel (Breyanzi), and tisagenlecleucel (Kymriah) can be considered established based on the clinically meaningful responses observed in DLBCL patients who have progressed or relapsed after previous treatment with the authorised CD19-directed CAR-T cell products in the third- and later lines setting. However, the claim of significant benefit of odronextamab over glofitamab (Columvi), epcoritamab (Tepkinly), and loncastuximab tesirine (Zynlonta) for the target patient population is not considered established based on the data presented. The sponsor should therefore further discuss the arguments for significant benefit over these three products for the target patient population and based on supplementary data.

3.4. COMP list of issues

The claim of significant benefit of odronextamab over glofitamab (Columvi), epcoritamab (Tepkinly), and loncastuximab tesirine (Zynlonta) for the target patient population is not considered established based on the data presented.

The sponsor should therefore provide additional data to support the claim of significant benefit for odronextamab versus these three products in patients with r/r DLBCL in the third- and later lines setting. Alternatively, the sponsor could consider indirect comparisons, such as matching-adjusted indirect comparisons versus Columvi, Tepkinly and Zynlonta.