# EU RISK MANAGEMENT PLAN ORDSPONO (ODRONEXTAMAB)

**RMP version to be assessed as part of this application:**

RMP Version number: 1.2

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|---|---|
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**Rationale for submitting an updated RMP**: Not applicable for the initial RMP

**Summary of significant changes in this RMP:** Not applicable

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**QPPV name**[1]: Dr. Suzanne Green

**QPPV oversight declaration:** The content of this RMP has been reviewed and approved by the marketing authorisation applicant's QPPV. The electronic signature is available on file.

[1] QPPV name will not be redacted in case of an access to documents request; see HMA/EMA Guidance document on the identification of commercially confidential information and personal data within the structure of the marketing-authorisation application; available on EMA website http://www.ema.europa.eu

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# LIST OF ABBREVIATIONS

| Abbreviation or Term | Definition/Explanation |
|---|---|
| ALT | Alanine aminotransferase |
| AST | Aspartate aminotransferase |
| ASTCT | American Society for Transplantation and Cellular Therapy |
| ATC | Anatomic Therapeutic Chemical |
| B-NHL | B-cell non-Hodgkin lymphoma |
| bsAb | Bispecific antibody |
| CAR-T | Chimeric antigen receptor T-cells |
| CHOP | Cyclophosphamide, doxorubicin, vincristine, prednisone |
| CI | Confidence interval |
| CMV | Cytomegalovirus |
| CNS | Central nervous system |
| COVID-19 | Coronavirus disease 2019 |
| CR | Complete response |
| CRS | Cytokine release syndrome |
| CVP | Cyclophosphamide, vincristine, prednisone |
| DLBCL | Diffuse large B-cell lymphoma |
| DOR | Duration of response |
| DP | Drug product |
| EEA | European Economic Area |
| EMA | European Medicines Agency |
| ESMO | European Society for Medical Oncology |
| EPAR | European Public Assessment Report |
| EU | European Union |
| FL | Follicular lymphoma |
| FLIPI | Follicular Lymphoma International Prognostic Index |
| GLP | Good Laboratory Practices |
| HBV | Hepatitis B virus |
| HCV | Hepatitis C virus |
| HD-ASCT | High dose therapy with autologous stem cell transplantation |
| HIV | Human immunodeficiency virus |
| ICANS | Immune effector cell-associated neurotoxicity syndrome |
| ICH | International Council for Harmonisation |
| ICR | Independent central review |
| IgG | Immunoglobulin G |
| IL-6 | Interleukin-6 |
| INN | International Non-proprietary Name |
| IRR | Infusion-related reaction |
| IV | Intravenous |
| IVIG | Intravenous immunoglobulin |
| KLH | Keyhole limpet hemocyanin |
| MAA | Marketing Authorisation Applicant |
| mAb | Monoclonal antibody |
| MCL | Mantle cell lymphoma |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MHC | Major histocompatibility complex |
| MOA | Mechanism of action |
| MTD | Maximum tolerated dose |
| MZL | Marginal zone lymphoma |
| NHL | Non-Hodgkin lymphoma |
| NHP | Non-Human Primate |
| NOS | Not otherwise specified |

| | |
|---|---|
| OBD | Optimal biological dose |
| OR | Odds ratio |
| ORR | Objective response rate |
| OS | Overall survival |
| PFS | Progression free survival |
| PI3K | Phosphatidylinositol 3-kinase |
| PL | Package Leaflet |
| PML | Progressive multifocal leukoencephalopathy |
| PSUR | Periodic Safety Update Report |
| PT | Preferred term |
| QPPV | Qualified person responsible for pharmacovigilance |
| QW | Weekly |
| R-CHOP | Cyclophosphamide, doxorubicin, prednisone, rituximab, vincristine |
| R-DHAP | Rituximab, dexamethasone, cytarabine, cisplatin |
| R-ICE | Rituximab, ifosfamide, carboplatin, etoposide phosphate |
| RMP | Risk Management Plan |
| RP2D | Recommended phase 2 dose |
| R/R | Relapsed or refractory |
| SEER | Surveillance, Epidemiology, and End Results |
| SIR | Standardised incidence ratio |
| SmPC | Summary of Product Characteristics |
| SOC | System organ class |
| TCR | T-cell receptor |
| TLS | Tumour lysis syndrome |
| ULN | Upper limit of normal |
| US | United States |

# PART I PRODUCT(S) OVERVIEW

**Table Part I.1: Product Overview**

| | |
|---|---|
| **Active substance(s) (INN or common name)** | Odronextamab (REGN1979) |
| **Pharmacotherapeutic group(s) (ATC Code)** | Not yet assigned |
| **Marketing Authorisation Holder or Applicant** | Regeneron Ireland DAC |
| **Medicinal products to which this RMP refers** | Odronextamab |
| **Invented name(s) in the EEA** | ORDSPONO |
| **Marketing authorisation procedure** | Centralised procedure |
| **Brief description of the product** | Chemical class:<br>Odronextamab (REGN1979) is a recombinant human IgG4-based bispecific antibody. |
| | Summary of mode of action:<br>Odronextamab is a human IgG4-based bispecific antibody that binds to CD20, a B-cell surface antigen present on normal and malignant B-cells and CD3, a T-cell antigen associated with the T-cell receptor complex. Simultaneous engagement of both arms of odronextamab results in formation of a synapse between the T cell and the CD20 expressing cell, resulting in T-cell activation and generation of polyclonal cytotoxic T-cell response, which result in redirected lysis of the targeted cells, including malignant B cells. |
| | Important information about its composition:<br>Odronextamab is produced by recombinant DNA technology in Chinese hamster ovary cell suspension culture. |
| **Hyperlink to the Product Information** | Module 1.3.1, Combined Annexes |
| **Indication(s) in the EEA** | Current: Not applicable |
| | Proposed:<br>Odronextamab as monotherapy is indicated for the treatment of adult patients with R/R FL after two or more lines of systemic therapy. |

<table>
<tr><td></td><td>Odronextamab as monotherapy is indicated for the treatment of adult patients with R/R DLBCL, after two or more lines of systemic therapy.</td></tr>
<tr><td>Dosage in the EEA</td><td>Current: Not applicable</td></tr>
<tr><td></td><td>Proposed:<br>For Cycles 1 to 4, a treatment cycle is 21 days. Prophylaxis and premedication for the treatment of patients with R/R FL and R/R DLBCL are detailed in Section 4.2 of the SmPC. Odronextamab should be administered until disease progression or unacceptable toxicity.
<table>
<tr><td colspan="2"></td><td>R/R FL</td><td>R/R DLBCL</td><td></td></tr>
<tr><td colspan="2">Day of Treatment</td><td colspan="2">Dose of Odronextamab</td><td>Duration of infusion</td></tr>
<tr><td rowspan="6">Cycle 1 (Step-Up Dosing)</td><td>Day 1</td><td colspan="2">0.2 mg</td><td rowspan="6">Administer odronextamab as a 4-hour infusion.</td></tr>
<tr><td>Day 2</td><td colspan="2">0.5 mg</td></tr>
<tr><td>Day 8</td><td colspan="2">2 mg</td></tr>
<tr><td>Day 9</td><td colspan="2">2 mg</td></tr>
<tr><td>Day 15</td><td colspan="2">10 mg</td></tr>
<tr><td>Day 16</td><td colspan="2">10 mg</td></tr>
<tr><td rowspan="3">Cycles 2 to 4</td><td>Day 1</td><td>80 mg</td><td>160 mg</td><td rowspan="3">Administer odronextamab as a 4-hour infusion on Cycle 2, Day 1. If tolerated, for all subsequent doses starting on Cycle 2, Day 8, infusion time can be reduced to 1 hour.</td></tr>
<tr><td>Day 8</td><td>80 mg</td><td>160 mg</td></tr>
<tr><td>Day 15</td><td>80 mg</td><td>160 mg</td></tr>
<tr><td>Maintenance (every 2 weeks)</td><td>Begin 1 week after the end of Cycle 4</td><td>160 mg</td><td>320 mg</td><td>Administer odronextamab as a 1-hour infusion every two weeks until disease progression or unacceptable toxicity.</td></tr>
<tr><td>Maintenance (Every 4 weeks)</td><td>If a patient is in complete response (CR) for 9 months, administer the odronextamab maintenance dose every 4 weeks.</td><td>160 mg</td><td>320 mg</td><td>Administer odronextamab as a 1-hour infusion every 4 weeks until disease progression or unacceptable toxicity.</td></tr>
</table></td></tr>
<tr><td>Pharmaceutical form(s) and strengths</td><td>Current: Not Applicable</td></tr>
</table>

| | |
|---|---|
| | Proposed:<br>Odronextamab DP is formulated as a concentrate for solution for infusion. The list of excipients includes L-histidine, L-histidine monohydrochloride monohydrate, sucrose, Polysorbate 80, Water for injections. All odronextamab DP are supplied as a sterile liquid solution in glass vials. Odronextamab is a clear to slightly opalescent, colourless to pale yellow solution with a pH of 5.8.<br><br><u>Odronextamab 2 mg concentrate for solution for infusion</u><br>Each single-dose vial contains 2 mg of odronextamab in 1 mL at a concentration of 2 mg/mL.<br><br><u>Odronextamab 80 mg concentrate for solution for infusion</u><br>Each single-dose vial contains 80 mg of odronextamab in 4 mL at a concentration of 20 mg/mL.<br><br><u>Odronextamab 320 mg concentrate for solution for infusion</u><br>Each single-dose vial contains 320 mg of odronextamab in 16 mL at a concentration of 20 mg/mL.<br><br>Route of administration: IV |
| **Is/will the product be subject to additional monitoring in the EU?** | Yes |

# PART II SAFETY SPECIFICATION

# PART II: MODULE SI EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

NHL is a heterogenous group of haematological malignancies and is the 11th most commonly occurring cancer globally (Ferlay, 2020b). In 2020, an estimated 544,352 cases were diagnosed globally with an age-standardised incidence of 5.8 per 100,000 persons (Ferlay, 2020b) (Sung, 2021). The highest incidence of NHL is observed in countries with high human development indexes (Carbone, 2019) ( Ferlay, 2020b) (Marcos-Gragera, 2011). Geographical variations exist in the incidence and prevalence of NHL. In Europe alone, 122,979 new cases occurred in 2020, accounting for 22.6% of global NHL diagnosis (Ferlay, 2020a) (Ferlay, 2020b). The highest age-standardised incidence rates are observed in Australia/New Zealand (15.3 and 10.9 per 100,000 males and females respectively), Northern America (14.1 and 10.0 per 100,000 men and women respectively) and Northern Europe (13.4 and 9.5 per 100,000 men and women respectively) (Ferlay, 2020b) ( Sung, 2021). More than 90% of NHLs originate from B-cells while the remaining are from T/natural killer cells (Smith, 2015) (Teras, 2016). The 2 most common subtypes of NHLs are FL, which is indolent and slowly progressing, and DLBCL, which is aggressive and fast progressing (Cerhan, 2020).

**Indication: Follicular Lymphoma**

FL accounts for approximately 5% of haematologic malignancies and is the second most frequently occurring type of B-cell NHLs, accounting for 25% of all cases (Carbone, 2019) (Swerdlow, 2017) (Teras, 2016). The proportion of FL among NHL cases was found to be highest in North American (33.6%) and Western European (20%) countries compared to South-Eastern European countries (15.8%) (Dotlic, 2015).

In a cancer registry in the Netherlands, 1,028 NHL cases were diagnosed from June 1981 to December 1989 and the proportion of FL cases was 22.7% (Maartense, 2000). The proportion of FL cases among patients with NHL was similar in a German study, which pooled data from 11 cancer registries that represent about 40% of the German population (Pulte, 2013). In this study, 33,009 NHL cases were diagnosed between 2002 and 2006, among which approximately 22.9% represented FL cases. Data from 11 cancer registries representing about 40% of the German population were pooled together and 33,009 NHL cases were diagnosed between 2002 to 2006. Approximately 22.9% were FL cases. The proportion of FL cases from 595 new NHL cases identified in South-Eastern Europe from 2004 through 2010 was lower (Dotlic, 2015). These cases were assessed from 9 medical centres in Croatia, Romania, and Macedonia located in South-Eastern Europe and FL cases accounted for 16% of all diagnoses.

***Incidence***

A French population-based registry including 4,790 lymphoid malignancies diagnosed between 1980 and 2009 identified 384 (8%) FL cases, and the estimated world-age-standardised incidence rate was 1.8 per 100,000 population (Dandoit, 2015). In a province in Spain, the age-adjusted incidence rate of FL diagnosed over a 19-year period (1996 to 2015) was estimated to be 3.74 per 100,000 (Solans, 2019). Similarly, the age-standardised incidence rate was 3.70 per 100,000 from

years 2002 to 2013 in a different study using data from the Spanish Network of Cancer registries (REDECAN), which consists of population-based registries from 13 provinces (Pla, 2022). Using data from the EUROCARE network, NHL cases diagnosed from 2000 to 2002 were assessed from 44 population-based registries covering approximately 30% of the European population (Sant, 2010). The crude incidence rate of FL was 2.18 per 100,000 persons. The crude incidence was similar for the years 2000 to 2007 (2.19 per 100,000 persons) in the rare cancers project (RARECARE) in which data from 83 cancer registries across Europe were analysed (Gatta, 2017). Smith et al used estimates obtained from the population-based Haematological Malignancy Research Network covering 14 hospitals in the UK; FL comprised 923 (15.9%) of new cases of lymphomas diagnosed from 2004 to 2012 (Smith, 2015). The crude incidence rate was 3.23 per 100,000 and age-standardised rate was 2.81 per 100,000 (Smith, 2015). In a different study using the population-based National Cancer Registry data with a 100% coverage in Poland, FL made up 6.3% of all NHL cases diagnosed from 2000 to 2014 and the standardised incident rate was 0.87 per 100,000 persons (Szumera-Ciećkiewicz, 2020).

***Prevalence***

Based on the literature search performed by the Applicant, the prevalence of FL has been evaluated in 2 published studies covering populations in the UK and Sweden, which are summarised in Table Part II: Module SI.1. Three-, five-, and ten-year point prevalence estimates in the UK demonstrated an increase in prevalence of FL with longer periods. The ten-year prevalence was 25.2 in UK and 28.4 in Sweden (Smith, 2015). In Sweden, the 5-year prevalence of FL increased by 27% from 1,045 cases in 2004, to 1,328 cases in 2016 and on average increased annually by 2.6% (Ekberg, 2020).

**Table Part II: Module SI.1: Prevalence of Follicular Lymphoma from Published European Studies**

| Country/region | Year | No. of centres | Prevalence period | Prevalence (95% CI) per 100,000 | Author |
|---|---|---|---|---|---|
| **UK** | 2004 to 2012 | 14 hospitals | 3 years | 9.7 (8.7-10.7) | Smith et al. |
| | | | 5 years | 14.8 (13.6-16.1) | |
| | | | 10 years | 25.2 (23.5-26.9) | |
| **Sweden** | 2016 | Swedish lymphoma registry | 10 years | 28.4 (27.2-29.6) | Ekberg et al. |

***Demographics of the Population for the Proposed Indication - Age, Sex, Racial and/or Ethnic Origin and Risk Factors for the Disease***

Age: A study from the UK reported the overall median age at diagnosis of FL as 64.9 years (range: 55.8-73.7) (Smith, 2015). The median age at diagnosis among males was 63.1 years (range: 55-72.8 years) and it was higher in females (66.3 years [range: 56.5-73.8 years]). In Poland, the median age at diagnosis was slightly lower at 61 years, which was similar between males (60 years) and females (61 years) (Szumera-Ciećkiewicz, 2020). The overall median age at diagnosis using data from a province in Spain was 62.1 years (Solans, 2019). Likewise, in the Spanish registry data covering 13 provinces, the median age at FL diagnosis was 62 years (Pla, 2022).

Sex: There appears to be a modest predisposition towards greater incidence of FL in women, although some data suggests the opposite. In the UK , the age-standardised incidence rate in males was 2.73 per 100,000, while it was 2.89 per 100,000 in females (age-standardised rate ratio for males vs female: 0.95 [95% CI: 0.90-0.99]) (Smith, 2015). The crude incidence rate in males and

females was 2.1 and 2.26 per 100,000 persons, respectively, in the HAEMACARE study on European countries (Sant, 2010). In a Polish population-based registry, male FL cases accounted for 5.6% of NHL cases, while females accounted for 6.9% of FL cases (Szumera-Ciećkiewicz, 2020). Though the standardised incidence rate was similar in both males and females (0.87 per 100,000), the incidence in females increased significantly from 2000 to 2014. The male to female sex ratio was 0.94 in a Spanish study including data from 13 provinces (Pla, 2022). On the other hand, the rate of diagnosis was higher in men compared to women in a single registry study in Spain with an incidence ratio of 1.07 (Solans, 2019). Similarly, the incidence rate was higher in males (male to female sex ratio: 1.1:1), though not statistically significant, in a French registry of FL cases diagnosed between 1980 and 2009 (Dandoit, 2015).

Racial and/or ethnic origin: The SEER programme covers approximately 95% of the US population and provides incidence data by race and ethnicity. From 2011-2012, the age-adjusted incidence of FL was significantly higher for non-Hispanic White persons at 3.8 per 100,000 compared to non-Hispanic Black (1.5 per 100,000), Hispanic (2.8 per 100,000), and Asian/Pacific Islander (1.7 per 100,000) persons (Teras, 2016).

Genetic risk factors: In the InterLymph Subtypes Project, which utilised case-control studies from Europe, North America, and Australia, having a first degree relative with a history of haematological malignancy independently increased the risk of FL (Cerhan, 2015) (Fallah, 2016) ( Linet, 2014). Specifically, in persons with a first degree relative with NHL, FL odds were elevated by 2-fold (OR: 1.99, 95% CI:1.55-2.54) (Linet, 2014). The elevated risk of FL was similar to that seen in a study of 5 Scandinavian countries (Fallah, 2016). First degree family history of FL was associated with increased incidence of FL (SIR: 2.1, 95% CI: 1.3-3.4). Familial history of haematological malignancies and genome-wide association studies that identified potential gene variants of FL (Skibola, 2014) support the role of genetic factors in the development of FL.

Other risk factors for FL: The odds of FL were higher in overweight persons (body mass index, BMI: 25-<30) (OR: 1.49; 1.21-1.83) compared to persons with normal weight (BMI: 18.5 to <22.5) in a study in the InterLymph consortium comprising of 19 case-control studies from Australia, Europe, and North America (Linet, 2014).

***Main Treatment Options***

Treatments approved for FL vary by country and patient population (newly diagnosed FL versus R/R FL) as detailed in ESMO guidelines (Dreyling, 2021).

The treatment options approved in the EU for first-line therapy include the following:

- Anti-CD20 antibody (obinutuzumab or rituximab) with chemotherapy (eg, bendamustine, CHOP, or CVP)
- For patients who are elderly and considered unfit for the above regimens, treatment options include rituximab alone, chlorambucil or cyclophosphamide with or without rituximab, or ibritumomab tiuxetan

The treatment options approved in the EU for previously treated FL include the following:

- Lenalidomide in combination with rituximab
- CAR-T products (axicabtagene ciloleucel, tisagenlecleucel, lisocabtagene maraleucel)

- PI3K inhibitors (idelalisib and duvelisib)
- CD20xCD3 bispecific antibody (mosunetuzumab)
- Radioimmunotherapy

Despite the presence of multiple treatment options, FL remains an incurable disease, and patients typically relapse, requiring successive therapeutic options. Lenalidomide (REVLIMID®) in combination with rituximab is approved in the EU for the treatment of adult patients with previously treated FL. Lenalidomide with rituximab yielded a median PFS of 39 months in a phase 3 study of 358 patients (82% had FL; median 1 prior treatment), compared with 14 months with rituximab alone (Leonard, 2019). Of note, patients with rituximab-refractory disease were excluded in this study. Multiple relapses in FL are common, and remissions become shorter in depth and duration over time. In the third-line setting, available treatment options include certain treatment options approved for first- and/or second-line FL. However, patients who have become refractory to their prior therapies are unlikely to derive treatment benefit from re-using these therapies. Options for these patients include CAR-T products (axicabtagene ciloleucel, tisagenlecleucel, lisocabtagene maraleucel), CD20xCD3 bispecific antibody (mosunetuzumab), PI3K inhibitor therapy, and radioimmunotherapy. For patients who develop disease that is refractory to CD20 antibody, the approved treatment options in the EU at present are PI3K inhibitors (idelalisib and duvelisib) (Copiktra [Summary of Product Characteristics], 2020) (Zydelig [Prescribing Information], 2018). As a class of medications, the PI3K inhibitors used for treating patients with FL yield low CR rates between 1% to 8%. The utility of PI3K inhibitors for patients with FL is limited due to safety issues. In the US, idelalisib, duvelisib, and umbralisib were voluntarily withdrawn from their accelerated approvals for the treatment of patients who relapsed or were refractory to ≥2 prior lines of therapy. The FDA noted the repeated observation of a higher rate of death or concerning OS results in 6 randomised controlled trials evaluating PI3K inhibitors and raised safety concerns for the class of PI3K inhibitors (Richardson, 2022).

New treatment options such as CAR-T products have been recently approved. For example, axicabtagene ciloleucel has showed efficacy of 91% ORR, 77% CR, and 38.6 months DOR FL (Yescarta USPI, 2022). However, CAR-T products are associated with considerable risk of AEs for CRS and neurotoxicity. Further, CAR-T therapy is not feasible in all circumstances due to patient comorbidities and manufacturing delays. A recent conditional approval in the EU for the treatment of R/R FL after 2 prior lines of systemic therapy is mosunetuzumab, a CD3xCD20 bispecific antibody. Efficacy showed ORR of 80%, CR of 60%, and median DOR of 22.8 months (Lunsumio [Summary of Product Characteristics], 2022).

In summary, although existing therapies provide responses in some patients with R/R FL, the overall response rate (including CR rate) and PFS decreases with each line of therapy. Multiple relapses after successive lines of therapy are typical for this malignancy, and disease progression is the principal cause of death in patients with FL. Therapies that improve PFS and OS are lacking for patients with FL R/R.

***Natural History of the Indicated Condition in the Untreated Population, including Mortality and Morbidity***

FL is a slow growing geminal B-cell malignancy with an estimated median survival >15 years (Carbone, 2019). In the first few years following initial treatment, FL may relapse or progress to a more aggressive disease in about 20% of patients. Currently, there is no cure for FL, largely due

to the fact that its aetiology is not fully understood (Carbone, 2019). Chromosomal translocation of t(14;18) has been identified in more than 85% of FL tumours (Cerhan, 2020) and high circulating levels are associated with elevated FL risks (Roulland, 2014). In the SEER programme covering 18 cancer registries in the US, the estimated 5-year relative survival rates of FL ranged from 80 to 90% between 2000 and 2016 (Cerhan, 2020). In Europe, the overall 5-year relative survival of FL cases diagnosed from 2000 to 2002 was 72.8% (95% CI: 71.0% - 74.6%) (Marcos-Gragera, 2011). In the UK specifically, the 5-year OS of FL diagnosed from 2004 to 2012 was 75.6% (95% CI: 71.9% - 78.2%) while the relative survival was 86.5% (95% CI: 83% - 89.4%) (Smith, 2015). The 5-year survival rate was similar in a French-based population study (Dandoit, 2015), while the 5- and 10-year survival was estimated at 71% (66% to 75%) and 56% (51% to 61%) respectively. In patients with R/R FL, studies have shown a median OS of 68 months at third-line of treatment reducing to 43 months at fifth or more line of treatment (Ghione, 2023).

***Important Comorbidities***

As the mean age of patients with FL is >60 years old, common comorbidities include those expected in the general population greater than 60 years of age such as cardiovascular disorders, hypertension, chronic obstructive pulmonary disorder, and diabetes mellitus.

Although there are no existing broad regional data reporting comorbidities among patients with FL, country-specific studies have reported the prevalence of comorbidities observed among these patients. In a multicentre study in France, patients with R/R FL receiving treatment from 2013-2015 were identified as having comorbidities of cardiovascular disease (29.5%), diabetes (28.6%), and respiratory failure (9.8%) (Solal-Céligny, 2018). Other comorbidities including renal failure, history of thrombosis, and history of neuropathy were identified in 3% to 8% of the sample population. From 2000 to 2014, newly diagnosed patients with no history of lymphoma were identified from 3 medical institutions in Serbia. Approximately 39.4% of patients <60 years had at least 1 comorbidity and the prevalence was higher among patients older than 60 years (63.5%) (Mihaljevic, 2016). Overall, the most common comorbidities were arterial hypertension (16.5%), heart disease (14.7%), diabetes mellitus (8%), and autoimmune disorders (2.7%). Among patients recently diagnosed at a single centre in Japan in 2001-2014, the most common comorbidities included tumours without metastasis (19.5%), diabetes (14.2%), and connective tissue disease (7.1%). Other comorbidities included chronic pulmonary disease (5.3%), liver disease (4.4%), cardiac disease (4.4%), cerebrovascular disease (2.7%), ulcers (2.7%), metastatic solid tumours (1.8%), and peripheral vascular disease (0.9%) (Watanabe, 2015).

**Indication: Diffuse Large B-Cell Lymphoma**

DLBCL is the more frequently occurring and aggressive subtype of NHL (Cerhan, 2019) accounting for approximately one-third of all newly diagnosed cases. In the HAEMACARE project pooling data from 41 population-based registries in 20 European countries, 138,581 lymphoid malignancies were assessed from 2000 to 2002, out of which 18,685 were DLBCL cases (Marcos-Gragera, 2011). In a lymphoma registry in Sweden, about 35% of all NHL cases diagnosed were DLBCLs and the incidence increased significantly by 2.2% annually from 2000 to 2016 (Ekberg, 2020).

Combining data from 3 countries in South-Eastern Europe (Croatia, Romania, and Macedonia), DLBCL comprised 39% of all newly diagnosed NHL cases (Dotlic, 2015). In a German study, from 2002 to 2006, 33,009 NHL cases were identified from 11 cancer registries representing about

40% of the German population (Pulte, 2013). Approximately 27% were DLBCL cases. In the Netherlands, DLBCL cases (45.8%) were diagnosed from a cancer registry from June 1981 to December 1989 (Maartense, 2000). The proportion of DLBCL among NHL cases was found to be highest in South-Eastern European countries (39%) compared to North American (28.3%) and Western European (29.3%) countries (Anderson, 1998) ( Dotlic, 2015).

***Incidence***

In the US SEER data from 18 cancer registries, the age-adjusted incidence rate of DLBCL was 6.95 per 100,000 and the incidence increased significantly from 2000 to 2014 (Cerhan, 2019). In the UK, 2,373 (40.9%) of lymphomas diagnosed between 2004 and 2012 were identified as DLBCLs (Smith, 2015). The crude incidence rate was 8.31 per 100,000 and was 6.60 per 100,000 when standardised to the age distribution of the European population. From the HAEMACARE project, 44 registries identified DLBCL cases diagnosed from 2000 to 2002 (Sant, 2010) and the crude incidence rate was estimated at 3.81 per 100,000 persons. In a Polish population-based cancer registry, the standardised incidence rate was 2.65 per 100,000 for cases diagnosed from 2000 to 2014 (Szumera-Ciećkiewicz, 2020). Newly diagnosed lymphoid malignancies from 1980 and 2009 were assessed in France (Dandoit, 2015) and 4,790 malignancies were identified. The proportion of DLBCL was 13% and the age-standardised incidence rate was 2.6 per 100,000 population. In a province in Spain, the age-adjusted incidence rate of DLBCL cases diagnosed from 1996 to 2015 was 6.18 per 100,000 persons (Solans, 2019). In a larger Spanish study using data from the REDECAN, the age-adjusted incidence rate was similar at 6.04 per 100,000 persons (Pla, 2022). The projected adjusted rates for 2023 was 6.79 per 100,000. From the RARECARE project collating population-based registry data on rare cancers across multiple European countries (Rossi, 2015), the crude incidence of DLBCL for the years 2000 to 2007 was 4.32 per 100,000 persons (Kaplan, 2011).

***Prevalence***

The prevalence of DLBCL identified in European countries is provided in (Table Part II: Module SI.2). Based on a literature search performed by the Applicant, prevalence estimates have only been assessed for studies conducted within populations in the UK and Sweden (Table Part II: Module SI.2). Three-, five-, and ten-year point prevalence estimates in the UK demonstrated an increase in prevalence of DLBCL with longer periods. The ten-year prevalence estimates were 43.3 and 46.2 in UK and Sweden, respectively (Smith, 2015). In Sweden, the 5-year prevalence of DLBCL increased by 66% from 1,347 cases to 2,236 cases for diagnosis made between 2004 and 2016. On average, the prevalence increased annually by 3.9% (Ekberg, 2020).

**Table Part II: Module SI.2: Prevalence of DLBCL from Published European Studies**

| Country/region | Year | No. of centres | Prevalence period | Prevalence (95% CI) per 100,000 | Author |
|---|---|---|---|---|---|
| **UK** | 2004 to 2012 | 14 hospitals | 3 years | 17.6 (16.2-18.9) | Smith, 2015 |
| | | | 5 years | 25.9 (24.2-27.5) | |
| | | | 10 years | 43.3 (41.1-45.5) | |
| **Sweden** | 2016 | Swedish lymphoma registry | 10 years | 46.2 (44.7-47.7) | Ekberg, 2020 |

***Demographics of the Population for the Proposed Indication - Age, Sex, Racial and/or Ethnic Origin and Risk Factors for the Disease***

Age: Age is a recognised risk factor and DLBCL occurs mostly in older adults. In the UK, the overall median age at diagnosis was 70 years (range: 59.6-78.2 years) (Smith, 2015). Males were younger at diagnosis (median: 68.4 [range: 58-76.9 years]) compared to females (median: 71.4 years [range: 61.4-79.6 years]). The overall median age at diagnosis estimated from a province in Spain was 66.3 years (Solans, 2019). Combining data from multiple registries in Spain in the REDECAN project, the median age at diagnosis was 68 years (Pla, 2022). The median age at diagnosis was similar in France (69 years [range: 54-78 years]) for cases diagnosed between 1980 and 2009 (Dandoit, 2015).

Sex: DLBCL occurs more frequently in males than females. From 44 cancer registries across Europe, the crude incidence rate was 4.06 and 3.57 per 100,000 persons in males and females respectively (Sant, 2010). In Poland, the standardised incidence rate in males was 2.91 per 100,000 and 2.39 per 100,000 in females (Szumera-Ciećkiewicz, 2020). In the UK the age-standardised incidence rate in males was 7.85 per 100,000 while it was 5.60 per 100,000 females (age-standardised rate ratio: 1.40, 95% CI: 1.36 - 1.42) (Smith, 2015). Similarly, the incidence rate was 1.4 times higher in males than in females in a Spanish province (Solans, 2019) and male to female sex ratio was 1.16 in a different Spanish study including data from multiple provinces (Pla, 2022). In a French registry data assessing lymphoid malignancies diagnosed between 1980 and 2009 (Dandoit, 2015), the incidence in males was significantly higher compared to females (male to female sex ratio: 1.4:1).

Racial and/or ethnic origin: In the US based SEER cancer registry, the age-adjusted incidence rate for DLBCL diagnosed from 2000-2014 was similar for White (7.25 per 100,000) and Hispanic (7.3 per 100,000) persons (Cerhan, 2019). Though the rates were lower in Black persons (4.84 per 100,000) and Asian/Pacific Islanders (5.96 per 100,000), the incidence rate ratio compared to White persons was not significantly lower.

Genetic risk factors: A family history independently increases DLBCL risk by almost 2-fold (Cerhan, 2019) (Cerhan, 2014). In a large cohort of first degree relatives with NHL using population data from Sweden, Norway, Iceland, Finland, and Denmark, DLBCL risk was elevated among relatives with a history of NHL (Fallah, 2016). Specifically, persons with first degree relatives having a previous diagnosis of DLBCL were almost twice as likely to be diagnosed with DLBCL (standardised incidence ratio: 1.9, 95% CI: 1.4-2.6). Family history of a lymphoid malignancy increases NHL risk, suggesting an underlying genetic factor driving the development of DLBCL.

Other risk factors for DLBCL

Clinical risk factors have been identified to assess prognosis in patients with previously untreated DLBCL using the International Prognostic Index. Patients with 3 or more risk factors have a less than 50% chance of relapse-free survival and OS at 5 years. Although the International Prognostic Index was created prior to the adoption of anti-CD20 antibody therapy in standard front-line therapy of DLBCL, these risk factors were shown to be prognostic also in the era of anti-CD20 therapy in a Revised International Prognostic Index (Sehn, 2007). In addition, molecular markers have been identified that are known to be associated with adverse overall survival; these include the presence of chromosomal rearrangements involving the MYC and BCL-2 and/or BCL-6 coding regions, and other aggregated molecular genetic characteristics have also been shown to be prognostic (Schmitz, 2018) (Chapuy, 2018).

***Main Treatment Options***

Treatments approved for DLBCL vary by country and patient population (newly diagnosed DLBCL versus R/R DLBCL) as described in ESMO guidelines (Tilly, 2015).

The treatment options approved in the EU for first-line therapy include the following:

- Anti-CD20 antibody and an anthracycline-based regimen (often R-CHOP)
- For patients who are elderly and considered unfit for the above regimens, treatment options include rituximab alone, chlorambucil or cyclophosphamide with or without rituximab, or ibritumomab tiuxetan.

The treatment options approved in the EU for previously treated DLBCL include the following:

- Chemotherapy regimens (including R-ICE or R-DHAP)
- HD-ASCT
- CAR-T products (axicabtagene ciloleucel, tisagenlecleucel and lisocabtagene maraleucel)
- Anti-CD79b antibody drug conjugate, polatuzumab vedotin, in combination with bendamustine and rituximab
- CD19-directed cytolytic antibody, tafasitamab, in combination with lenalidomide
- CD20xCD3 T-cell engaging bispecific antibody (glofitamab and epcoritamab)
- CD19-directed antibody and alkylating agent conjugate (loncastuximab tesirine)

Although existing therapies provide responses in some patients with R/R DLBCL, the DOR is typically brief. Further, the overall response rate (including CR rate) and PFS decrease with each line of therapy. Multiple relapses after successive lines of therapy are typical for this malignancy, and disease progression is the principal cause of death in patients with DLBCL. Curative therapies that improve PFS and OS with an acceptable safety profile are lacking for patients with R/R DLBCL. There continues to be a need for therapies which can improve upon current standards and are accessible to patients.

***Natural History of the Indicated Condition in the Untreated Population, including Mortality and Morbidity***

DLBCL is a B-cell NHL with a complex molecular aetiology. It is a more aggressive subtype of NHL and progresses rapidly. The overall 5-year relative survival as estimated in HAEMACARE was 49.3% (95% CI: 47.8-50.6%) for cases diagnosed from 2000 to 2002 (Marcos-Gragera, 2011). The 5-year OS for cases diagnosed in the UK from 2004 to 2012 was 46.3% (44.2% to 48.4%) while the relative survival was 54.8% (52.4% to 57.1%) (Smith, 2015). In a population-based French study with data from 1980 to 2009, the 5-year survival was 46% (43% to 50%) while 10-year survival was 36% (32% to 40%) (Dandoit, 2015). In patients with R/R DLBCL treated with salvage therapy, studies have shown a median OS of 6.3 months (Crump, 2017) to 6.8 months (Van Le, 2023), and 1-year survival rate of 28% (Crump, 2017).

***Important Comorbidities***

In a medical centre in Austria, the most frequent comorbidities in recently diagnosed patients were previous solid tumour (9.4%), cardiovascular diseases including coronary artery disease, congestive heart failure and myocardial infarction (7.2%), renal disease (6.6%), diabetes (5.5%), and rheumatologic disease (3.3%). Heart valve disease, psychiatric disturbance, cerebrovascular disease, peptic ulcer, severe and pulmonary comorbidity, mild and severe liver disease occurred in 1% to 3% of the patient population (Kocher, 2020). In the Swedish Lymphoma Registry, 45% of adult patients diagnosed from 2007 to 2013 had one or more comorbidities. The most prevalent comorbidities were cardiovascular diseases (14%), solid cancers (13%), and diabetes (10%) (Wästerlid, 2019). Patients with R/R DLBCL undergoing leukapheresis for CAR-T-cell therapy were identified across 9 medical centres. Vascular diseases (51%), endocrine diseases (45%), and hypertension (43%) were the most common comorbidities (Shouse, 2021). At a clinic in the US from 2004 to 2014, the most commonly occurring comorbidities were diabetes (20%), coronary artery disease (18%), history of another cancer (17%), and connective tissue disease (8%) in recently diagnosed patients aged ≥60 years (Saygin, 2017).

# PART II: MODULE SII NONCLINICAL PART OF THE SAFETY SPECIFICATION

Key safety findings from nonclinical studies and relevance to human usage:

| Key Safety Finding | Relevance to human use |
|---|---|
| **Toxicity** | |
| **Single and repeat dose toxicity**<br>4 non-GLP single-dose studies were performed, administering a single IV dose of odronextamab to animals.<br>Observations: Rapid and sustained B-cell depletion in peripheral blood and lymphoid tissues, clinical signs consistent with infection. | Due to the mechanism of action of odronextamab, B-cell depletion could reasonably be anticipated in human use. |

| Key Safety Finding | Relevance to human use |
|---|---|
| A single-dose and escalating dose toxicity study in female cynomolgus monkeys was performed administering odronextamab IV and SC. Observations: Abnormal faecal observations leading to decreased body weight/thin condition consistent with cytokine release and/or presumed infection secondary to sustained B-cell depletion. Increases in cytokines correlated with non-formed faeces, vomiting, elevated temperature, and/or skin discoloration in 1 mg/kg animals. | Due to the mechanism of action of odronextamab, B-cell depletion could reasonably be anticipated in human use. As functional in vitro assays for cytokine release demonstrated that odronextamab had comparable activity in human and NHP cells, the effects on cytokine release are also relevant to human use. |
| A 4-week repeat dose toxicity study in cynomolgus monkeys was performed administering odronextamab once weekly. Observations: Odronextamab induced sustained B-cell depletion in peripheral blood and lymphoid organs at all dose levels. Transient decrease in T cells, followed by slight T-cell activation. Increased cytokine levels postdose on day 1 correlated with clinical observation of vomitus. Clinical pathology findings were consistent with inflammation. | Due to the mechanism of action of odronextamab, B-cell depletion is considered a pharmacological effect of odronextamab and could reasonably be anticipated in human use. Functional in vitro assays for T-cell proliferation and cytokine release demonstrated odronextamab had comparable activity in human and NHP cells. |
| A 16-week repeat dose toxicity study in cynomolgus monkeys was performed administering odronextamab IV, once weekly. Observations: B-cell depletion in peripheral blood seen at all dose levels. Dose-dependent increases in proinflammatory cytokines were observed postdose on day 1 only and decreased by 24 hours postdose. Clinical observations consistent with presumed infections; body weight losses, decreased food consumption, dehydration, hypoactivity, and/or thin body conditions, and clinical pathology effects consistent with acute inflammation including | Due to the pharmacological effect of odronextamab, effect on B-cell depletion may be expected in human use. Because of the demonstrated relevancy of NHP to human models, effects on cytokines may be considered relevant to human use. |

| Key Safety Finding | Relevance to human use |
|---|---|
| mixed-cell inflammation and mononuclear cell infiltrates of several tissues. | |
| **Reproductive toxicity** | |
| Fertility endpoints were evaluated during the 16-week repeat dose toxicology study conducted in monkeys. There were no odronextamab-related findings in fertility endpoints or microscopic assessment of reproductive organs at doses of up to and including 1 mg/kg/week IV. No reproductive toxicology studies have been conducted with odronextamab. | Based on its mechanism of action, odronextamab may cause fetal B-cell lymphocytopenia when administered to a pregnant woman. Odronextamab causes T-cell activation and cytokine release; immune activation may compromise pregnancy maintenance. |
| **Developmental toxicity** | |
| No developmental toxicology studies have been conducted with odronextamab.<br>Developmental toxicity studies (pre- and postnatal development studies) are generally not applicable to therapies for advanced cancer indications (ICH S9). Embryo-fetal developmental toxicology studies with odronextamab were not conducted as such studies are expected to have limited value in further understanding and communicating risks to patients with advanced cancer. | Developmental toxicity, including pregnancy and lactation, was not considered essential to inform risk to pregnant women based on the intended patient population. |
| **Genotoxicity** | |
| According to the ICH Guideline (ICH S6[R1], 2011), the standard genotoxicity studies routinely conducted for small-molecule pharmaceuticals are not applicable to biotechnology-derived pharmaceuticals. Antibodies, such as odronextamab, are not expected to interact directly with DNA or other chromosomal material. | Odronextamab is not expected to be genotoxic. |

| Key Safety Finding | Relevance to human use |
|---|---|
| **Carcinogenicity** | |
| No standard carcinogenicity studies were conducted with odronextamab.<br>Standard carcinogenicity studies are generally not applicable to therapies for advanced cancer indications (ICH S9). | Odronextamab is not expected to be carcinogenic. |
| **Safety pharmacology** | |
| **Cardiovascular system including potential for QT prolongation** | |
| No cardiovascular effects were identified at doses up to 1 mg/kg/week in 4- and 16-week cynomolgus monkey studies. | Based on the nonclinical data, odronextamab is not expected to affect cardiovascular function or induce QT prolongation. |
| **Nervous system** | |
| No nervous system effects were identified at doses up to 1 mg/kg/week in 4- and 16-week cynomolgus monkey studies. | Neurotoxicity has been observed with T-cell engaging therapies such as CAR-Ts. |
| **Respiratory** | |
| No respiratory system effects were identified at doses up to 1 mg/kg/week in 4- and 16-week cynomolgus monkey studies. | Based on the nonclinical data, odronextamab is not expected to affect respiratory function. |
| **Hepatoxicity** | |
| No hepatotoxicity was identified in the clinical and anatomic pathology assessments in a 4- and 16-week cynomolgus monkey study. | Based on the nonclinical data, odronextamab is not expected to be hepatotoxic. |

| Key Safety Finding | Relevance to human use |
|---|---|
| **Other toxicity related information or data** | |
| **T-Cell dependent antibody response** | |
| Following KLH challenge in the 16-week study, no anti-KLH IgM or IgG responses were detected in animals administered odronextamab, consistent with its intended pharmacology of B-cell depletion. | Consistent with the intended pharmacology (B-cell depletion) odronextamab suppressed antibody responses against the antigen KLH. KLH data in animals is relevant to the expected response in vaccines. |
| **Cytokine release** | |
| Cytokine release was a parameter measured as a readout for T-cell activation across several nonclinical assays and studies performed that demonstrate the MOA. | Functional in vitro assays for T-cell proliferation and cytokine release demonstrated odronextamab had comparable activity in both monkeys and humans. |
| **Tissue cross-reactivity** | |
| In 2 GLP tissue cross-reactivity studies, biotinylated odronextamab (REGN1979-Bio) at 2 concentrations (2 and 10 µg/mL) was applied to cryosections from panels of normal human and cynomolgus monkey tissues and selected fetal human tissues. | No unanticipated cross-reactivity of odronextamab was observed in either study. |

**Summary of nonclinical safety concern**

**Important identified risks:** none

**Important potential risks:** none

**Missing information:** none

# PART II: MODULE SIII CLINICAL TRIAL EXPOSURE

## SIII.1 Overview of Development

In this EU RMP, the safety of odronextamab in patients with R/R FL and R/R DLBCL is supported by 2 open-label, multicentre studies (Study R1979-HM-1333 [Study 1333] and Study R1979-ONC-1625 [Study 1625]). Patients initiated treatment with step-up doses of odronextamab (either 1/20 mg or 0.7/4/20 mg) in cycle 1, followed by (80 mg for R/R FL and 160 mg for R/R DLBCL)

dosing on days 1, 8, and 15 for cycles 2 to 4, followed by dosing every 2 weeks (160 mg for R/R FL and 320 mg for R/R DLBCL). Unless otherwise stated in this EU RMP, data are presented for both dosing regimens.

Study 1625 is an ongoing open-label, single-arm, multicentre, phase 2 study of odronextamab monotherapy in patients with B-NHL; it has 5 disease-specific cohorts: FL grade 1-3a, DLBCL, MCL, MZL, and other B-NHL (comprising aggressive B-NHL subtypes not included in the other 4 cohorts) that are R/R to prior systemic therapy. The primary objective in this study is to assess the antitumour activity of odronextamab administered as an IV infusion as measured by ORR by ICR according to the Lugano Classification of response in malignant lymphoma B-NHL subgroups. A secondary endpoint in this study is to assess the safety and tolerability of odronextamab administered as an IV infusion. The data cutoff date for Study 1625 was 20 Oct 2023.

Study 1333 is an ongoing, first-in-human, open-label, single-arm, multicentre, phase 1 dose finding and dose escalation study of odronextamab monotherapy in patients with CD20+ B-cell malignancies (including FL and DLBCL) previously treated with CD20-directed antibody therapy. The study consists of a dose escalation phase and an expansion phase in disease-specific cohorts. The primary objectives of the study are to assess the safety, tolerability, and dose limiting toxicities of odronextamab administered as an IV infusion to determine the MTD and/or OBD as RP2D, to evaluate the odronextamab concentrations that could have correlated with observed toxicity and potential antitumour activity, and to study the antitumour activity of odronextamab in the DLBCL after failure of CAR-T therapy in an expansion cohort as measured by ORR by ICR according to the Lugano Classification of response in malignant lymphoma and assessed by independent central review. The data cutoff date for Study 1333 was 19 Sep 2023.

The odronextamab RP2D for investigation was 80 mg for patients with FL grade 1-3a and 160 mg for patients with DLBCL. Up to global Protocol Amendment 3 (study 1625) and Protocol Amendment 16 (study 1333), odronextamab was administered with a step-up regimen of 1/20 mg (the "1/20 regimen") from week 1 through week 3. In view of the observed incidence of grade ≥3 CRS events, the step-up regimen was modified during the course of the studies to 0.7/4/20 mg from week 1 through week 4 (the "0.7/4/20 regimen").

This RMP includes data from patients with R/R FL grade 1-3a and patients with R/R DLBCL who were enrolled in 80 mg QW IV and 160 mg QW IV cohorts, respectively, and had received at least 1 dose of odronextamab. Analyses for FL and DLBCL were performed separately. At the time of the data cutoff, the FL 80 mg Pool included 153 patients from Study 1625 or Study 1333. The DLBCL 160 mg Pool included 219 patients from Study 1625 and Study 1333.

## SIII.2 Clinical Trial Exposure

### FL 80 mg QW Pool

As of the clinical data cutoff date, the median duration of exposure for odronextamab 80 mg among patients with FL (from studies 1333 and 1625) was 38.14 (range: 0.4 to 195.7) weeks, with 98/153 (64.1%) patients exposed to odronextamab for ≥24 weeks. A median of 24.00 (range: 1.0 to 73.0) doses were administered. The median relative dose intensity from initial dose to first full dose was 100.00%, as was the median relative dose intensity from second full dose and beyond.

**DLBCL 160 mg QW Pool**

As of the clinical data cutoff date, the median duration of exposure for odronextamab 160 mg among patients with DLBCL (from studies 1333 and 1625) was 13.43 (range: 0.6 to 176.1) weeks, with 125/219 (57.1%) patients exposed to odronextamab for ≥12 weeks. A median of 15.00 (range: 1.0 to 65.0) doses were administered. The median relative dose intensity from initial dose to first full dose was 100.00%, as was the median relative dose intensity from second full dose and beyond.

Cumulative duration of exposure is presented in Table Part II: Module SIII.3.

Duration of exposure in patient time, and by age and gender, is presented for the patients with FL in Table Part II: Module SIII.4 and Table Part II: Module SIII.6, and for the patients with DLBCL in Table Part II: Module SIII.5 and Table Part II: Module SIII.7.

**Table Part II: Module SIII.3: Cumulative Duration of Exposure**

| **Duration of exposure (FL 80 mg QW Pool)[a]** | **Patients** | **Patient-years** |
|---|---|---|
| 1/20/80 mg | 74 | 78.85 |
| 0.7/4/20/80 mg | 79 | 60.82 |
| Total person time for indication | 153 | 139.67 |
| | | |
| **Duration of exposure (DLBCL 160 mg QW Pool)[a]** | **Patients** | **Patient-years** |
| 1/20/160 mg | 101 | 54.65 |
| 0.7/4/20/160 mg | 118 | 49.54 |
| Total person time for indication | 219 | 104.19 |

DLBCL, Diffuse large B-cell lymphoma; FL, Follicular lymphoma; QW, weekly.
[a] Data cutoff date is 20 Oct 2023 for Study 1625 and 19 Sep 2023 for Study 1333.

**Table Part II: Module SIII.4: Duration of Exposure in Patient Time (Safety Analysis Set), FL Grade 1-3a Patients 80 mg QW**

| Duration of exposure | Total (N=153) Number of Patients | Total (N=153) Patient time (Patient-year) |
|---|---|---|
| 0 - < 4 weeks | 10 | 0.42 |
| 4 - < 8 weeks | 4 | 0.42 |
| 8 - < 12 weeks | 11 | 2.03 |
| 12 - < 16 weeks | 16 | 4.15 |
| 16 - < 20 weeks | 7 | 2.59 |
| 20 - < 24 weeks | 7 | 2.95 |
| 24 - < 28 weeks | 10 | 4.99 |
| 28 - < 32 weeks | 7 | 3.93 |
| 32 - < 36 weeks | 2 | 1.32 |
| 36 - < 48 weeks | 17 | 13.82 |
| 48 - < 60 weeks | 11 | 11.66 |
| 60 - < 72 weeks | 13 | 16.63 |
| 72 - < 84 weeks | 17 | 24.87 |
| 84 - < 96 weeks | 9 | 15.45 |
| 96 - < 108 weeks | 0 | 0 |
| 108 - < 120 weeks | 2 | 4.24 |
| 120 - < 132 weeks | 2 | 4.83 |
| 132 - < 144 weeks | 2 | 5.3 |
| 144 - < 156 weeks | 0 | 0 |
| 156 - < 168 weeks | 2 | 6.22 |
| 168 - < 180 weeks | 2 | 6.51 |
| 180 - < 192 weeks | 1 | 3.58 |
| 192 - < 204 weeks | 1 | 3.75 |
| **Total patient time (Patient-year)** | **153** | **139.67** |

FL, Follicular lymphoma; QW, weekly.
Study 1625 data cut-off date is 20 Oct 2023. Study 1333 data cut is 19 Sep 2023.
Duration of treatment exposure (weeks) = [minimum (date of last dose + 14, data cutoff date+1, date of death+1) - date of first dose]/7
Patient time (Patient-year) = sum of patients duration of treatment exposure (years)

**Table Part II: Module SIII.5: Duration of Exposure in Patient Time (Safety Analysis Set), DLBCL Patients 160 mg QW**

| Duration of exposure | Total (N=219) Number of Patients | Total (N=219) Patient time (Patient-year) |
|---|---|---|
| 0 - < 4 weeks | 37 | 1.61 |
| 4 - < 8 weeks | 32 | 3.34 |
| 8 - < 12 weeks | 25 | 4.81 |
| 12 - < 16 weeks | 26 | 6.66 |
| 16 - < 20 weeks | 18 | 6.31 |
| 20 - < 24 weeks | 20 | 8.54 |
| 24 - < 28 weeks | 9 | 4.51 |
| 28 - < 32 weeks | 4 | 2.32 |
| 32 - < 36 weeks | 5 | 3.21 |
| 36 - < 48 weeks | 8 | 6.1 |
| 48 - < 60 weeks | 9 | 9.17 |
| 60 - < 72 weeks | 8 | 10.24 |
| 72 - < 84 weeks | 6 | 8.93 |
| 84 - < 96 weeks | 2 | 3.36 |
| 96 - < 108 weeks | 3 | 5.82 |
| 108 - < 120 weeks | 1 | 2.19 |
| 120 - < 132 weeks | 2 | 4.79 |
| 132 - < 144 weeks | 1 | 2.63 |
| 144 - < 156 weeks | 1 | 2.96 |
| 156 - < 168 weeks | 0 | 0 |
| 168 - < 180 weeks | 2 | 6.69 |
| **Total patient time (Patient-year)** | **219** | **104.19** |

DLBCL, Diffuse large B-cell lymphoma; QW, weekly.
Study 1625 data cut-off date is 20 Oct 2023. Study 1333 data cut is 19 Sep 2023.
Duration of treatment exposure (weeks) = [minimum (date of last dose + 14, data cutoff date+1, date of death+1) - date of first dose]/7
Patient time (Patient-year) =sum of patients duration of treatment exposure (years)

**Table Part II: Module SIII.6: Duration of Exposure in Patient Time by Age and Gender, FL Grade 1-3a 80 mg QW Patients (Safety Analysis Set)**

| Age group | Total (N=153) Number of Patients M | Total (N=153) Number of Patients F | Total (N=153) Patient time (Patient-year) M | Total (N=153) Patient time (Patient-year) F |
|---|---|---|---|---|
| <65 | 51 | 40 | 48.85 | 40.95 |
| 65-74 | 21 | 25 | 19.46 | 20.78 |
| 75-84 | 10 | 6 | 4.82 | 4.81 |
| Total | 82 | 71 | 73.13 | 66.54 |

F, female; FL, Follicular lymphoma; M, male; QW, weekly.
Study 1625 data cut-off date is 20 Oct 2023. Study 1333 data cut is 19 Sep 2023.
Patient time (Patient-year) =sum of patients duration of treatment exposure (years)

**Table Part II: Module SIII.7: Duration of Exposure in Patient Time by Age and Gender, DLBCL 160 mg QW Patients (Safety Analysis Set)**

| Age group | Total (N=219) Number of Patients M | Total (N=219) Number of Patients F | Total (N=219) Patient time (Patient-year) M | Total (N=219) Patient time (Patient-year) F |
|---|---|---|---|---|
| <65 | 65 | 35 | 33.12 | 20.03 |
| 65-74 | 42 | 34 | 13.23 | 14.44 |
| 75-84 | 25 | 14 | 15 | 6.43 |
| 85+ | 2 | 2 | 0.68 | 1.25 |
| Total | 134 | 85 | 62.03 | 42.16 |

DLBCL, Diffuse large B-cell lymphoma; F, female; M, male; QW, weekly.
Study 1625 data cut-off date is 20 Oct 2023. Study 1333 data cut is 19 Sep 2023.
Patient time (Patient-year) =sum of patients duration of treatment exposure (years)

# PART II: MODULE SIV POPULATIONS NOT STUDIED IN CLINICAL TRIALS

## SIV.1 Exclusion Criteria in Pivotal Clinical Studies within the Development Programmes

**Important Exclusion criteria in pivotal clinical trials across the development programme**

| **Criterion 1** | **Pregnant or breastfeeding women, and sexually active men and women of childbearing potential who were unwilling to use highly effective contraception prior to the initial dose/start of the first treatment, during the study and up to 6 months after the last dose** |
|---|---|
| Reason for being an exclusion criterion | Per ICH guidelines, pregnant women and breastfeeding women should normally be excluded from clinical trials.<br>No reproductive and developmental toxicology studies have been conducted with odronextamab.<br>Pregnant women were excluded to avoid potential harm to an unborn foetus.<br>There is no information regarding the presence of odronextamab in human milk, the effects on the breastfed infant, or the effects on milk production. |
| Considered to be missing data (Yes/No) | No |
| Rationale (if not included as missing information) | Pregnancy and breastfeeding are uncommon in this patient population, and thus use in these patients is not considered missing information. Adequately addressed in Section 4.6 of the SmPC. |
| **Criterion 2** | **HIV or uncontrolled infection with HBV, or HCV infection; or other uncontrolled infection** |
| Reason for being an exclusion criterion | It is common clinical practice to exclude patients with uncontrolled HIV, HBV, or HCV infections from clinical trials on anticancer therapy because of the potential to increase the risk of severe adverse events in these patients and confound the interpretation of safety. |
| Considered to be missing data (Yes/No) | No |

| | |
|---|---|
| Rationale (if not included as missing information) | It is consistent with standard of care to not include patients with active infections. Addressed in Section 4.4 of the SmPC. |
| **Criterion 3** | **Evidence of significant concurrent disease or medical condition, including but not limited to significant cardiovascular disease (eg, New York Heart Association Class III or IV cardiac disease, myocardial infarction within the previous 6 months, unstable arrhythmias, or unstable angina) and/or significant pulmonary disease (eg, obstructive pulmonary disease and history of symptomatic bronchospasm).** |
| Reason for being an exclusion criterion | It is common clinical practice not to include patients with significant concurrent disease or medical condition that could interfere with the conduct of the study or put the patient at significant risk. |
| Considered to be missing data (Yes/No) | No |
| Rationale (if not included as missing information) | There are no specific data on the use of odronextamab in patients with significant concurrent disease or medical condition. The treating physician would be expected to assess the benefit/risk balance for each patient.<br>FL and DLBCL indications affect older populations who may have several comorbidities. This exclusion criterion is based on the opinion of investigators for the purpose of clinical trials and will not represent a clearly distinct population in the post-approval setting. |
| **Criterion 4** | **History of severe allergic reaction attributed to compounds with a similar chemical or biologic composition as that of the study drug or excipient.** |
| Reason for being an exclusion criterion | Possible confounding of safety data. |
| Considered to be missing data (Yes/No) | No |
| Rationale (if not included as missing information) | Odronextamab is contraindicated in patients with prior history of hypersensitivity to odronextamab or any of its excipients. See Section 4.3 of the SmPC. |

| | |
|---|---|
| **Criterion 5** | **Known hypersensitivity to both allopurinol and rasburicase** |
| Reason for being an exclusion criterion | Patients considered to be at risk for TLS should receive prophylaxis with allopurinol or rasburicase prior to first administration of odronextamab |
| Considered to be missing data (Yes/No) | No |
| Rationale (if not included as missing information) | Adequately addressed in Section 4.2 of the SmPC |
| **Criterion 6** | **Primary CNS lymphoma or known involvement by non-primary CNS NHL** |
| Reason for being an exclusion criterion | Neurologic toxicities have been reported with bispecific antibodies and CAR-T therapies. Therefore, inclusion of patients with known CNS involvement may increase their risk of neurologic toxicities. |
| Considered to be missing data (Yes/No) | No |
| Rationale (if not included as missing information) | There are no specific data on the use of odronextamab in patients with active CNS involvement. The treating physician would be expected to evaluate the benefit and risks for each individual patient. |
| **Criterion 7** | **Concurrent active malignancy for which the patient is receiving treatment (Study 1333).**<br>**Another malignancy except B-NHL in the past 5 years, with the exception of non-melanoma skin cancer that has undergone potentially curative therapy or in situ cervical carcinoma, or any other tumour that has been deemed to be effectively treated with definitive local control and with curative intent (Study 1625).** |
| Reason for being an exclusion criterion | It is common clinical practice to exclude patients with other active malignancies from clinical trials as different anti-cancer treatments and the risk of progression for each malignancy precludes assessment of safety and efficacy of the investigational agent. |
| Considered to be missing data (Yes/No) | No |

| | |
|---|---|
| Rationale (if not included as missing information) | Consistent with standard of care. |

## SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

## SIV.3 Limitations in Respect to Populations Typically Under-Represented in Clinical Trial Development Programmes

**Table Part II: Module SIV.1: Exposure of Special Populations Included or Not in Clinical Trial Development Programmes**

| Type of Special Population | Exposure |
|---|---|
| Pregnant or breastfeeding women | Not included in the clinical development programme |
| Patients with hepatic impairment | Patients with inadequate hepatic function were excluded. The studies included patients who met the following hepatic function parameters:<br>• Total bilirubin ≤1.5 × ULN<br>• ALT and AST ≤2.5 × ULN |
| Patients with renal impairment | Patients with inadequate renal function were excluded. The studies included patients who met the following renal function parameters:<br>• Serum creatinine ≤1.5 × ULN, or calculated creatinine clearance by Cockcroft-Gault formula ≥50 mL/min. |
| Patients with cardiovascular impairment | Patients with inadequate cardiovascular health were excluded as evidenced by a cardiac ejection fraction <40% by echocardiogram or multi-gated acquisition scan. Additionally, patients with significant cardiovascular disease (eg, New York Heart Association Class III or IV cardiac disease, myocardial infarction within the previous 6 months, unstable arrhythmias, or unstable angina) were excluded. |

| Type of Special Population | Exposure |
|---|---|
| Immunocompromised patients | Not included in the clinical development programme. Patients with HIV who had controlled infection (undetectable viral load and CD4 count above 350 cells/microliter either spontaneously or on a stable antiviral regimen) were permitted. |
| Patients with a disease severity different from inclusion criteria in clinical trials | Not included in the clinical development programme |
| Population with relevant different ethnic origin | The studies did not exclude patients based on ethnicity or race. |
| Subpopulations carrying relevant genetic polymorphisms | The studies did not exclude patients with any specific genetic polymorphisms. |

# PART II: MODULE SV POST-AUTHORISATION EXPERIENCE

Not Applicable.

# PART II: MODULE SVI ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

**Potential for misuse for illegal purposes**

Based on the molecular structure, pharmacokinetics, and known mechanism of action of odronextamab, it is unlikely that odronextamab has any potential for misuse for illegal purposes. Additionally, odronextamab will be administered in a controlled clinical setting by healthcare professionals.

# PART II: MODULE SVII IDENTIFIED AND POTENTIAL RISKS

## SVII.1 Identification of Safety Concerns in the Initial RMP Submission

The important identified and potential risks for odronextamab have been determined based on observation in preclinical toxicology or clinical studies with odronextamab; risks reported with T-cell engaging immunotherapies; as well as risks generally associated with mAbs.

### SVII.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

**Reason for not including an identified or potential risk in the list of safety concerns in the RMP:**

| **Risks not included in the list of Safety Concerns in the RMP** |
|---|
| Risks with minimal clinical impact on patients (in relation to the severity of the indication treated): |
| The following ADRs, although reported frequently in the combined FL and DLBCL cohorts, have generally been low grade transient events and are unlikely to impact the benefit risk balance:<br>• Pyrexia was reported in 146/372 (39.2%) of patients, grade 3 or 4 in 10/372 (2.7%) patients.<br>• Abdominal pain was reported in 65/372 (17.5%) of patients, grade 3 or 4 in 8/372 (2.2%) patients.<br>• Diarrhea was reported in 96/372 (25.8%) of patients, grade 3 or 4 in 6/372 (1.6%) patients.<br>• Rash was reported in 85/372 (22.8%) patients, grade 3 or 4 in 10/372 (2.7%) patients.<br>• Insomnia was reported in 58/372 (15.6%) patients, grade 3 or 4 in 1/372 (0.3%) patients. |

- Hypotension was reported in 51/372 (13.7%) patients, grade 3 or 4 in 11/372 (3.0%) patients.
- Tachycardia was reported in 36/372 (9.7%) patients, grade 3 or 4 in 4/372 (1.1%) patients.
- Oedema was reported in 70/372 (18.8%) of patients, grade 3 or 4 in 7/372 (1.9%) of patients.
- Infusion related reactions were reported in 76/372 (20.4%) of patients, grade 3 in 7/372 (1.9%) of patients. With the recommended 0.7/4/20 mg step up regimen 28/197 (14.2%) of patients experienced infusion related reactions, grade 3 in 3/197 (1.5%) of patients. No grade 4 events were reported.

Adverse reactions with clinical consequences even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated:

*Tumour lysis syndrome*

Patients considered most at risk for TLS include those with a leukemic component with a high circulating lymphocyte/lymphoblast count and aggressive B-NHL with a high tumor burden (including bone marrow and extra medullary organ involvement).

No patients (0/197) with FL or DLBCL treated with the recommended step-up regimen (0.7/4/20 mg) experienced TLS following odronextamab dosing. Two out of 175 patients (1.1%) experienced TLS on the 1/20 step-up regimen (1 patient in the FL cohort and 1 patient in the DLBCL cohort, both grade 3 that resolved).

TLS can be an oncologic emergency when it occurs, however it is reliably recognised and well understood by healthcare professionals managing patients with haematologic malignancies. Haematologists routinely assess patients for the risk of TLS prior to the start of any treatment, and TLS prophylaxis is administered as appropriate in patients considered at risk.

Known risks that require no further characterisation and are followed up via routine pharmacovigilance and for which the risk minimisation messages in the product information are adhered by prescribers (eg, Actions being part of standard clinical practice in each EU member State where the product is authorised):

The following ADRs are expected in the patient population and are well known by treating physicians and can be appropriately managed: cytopenia, electrolyte abnormalities, and transient liver enzyme elevations.

Known risks that do not impact the risk-benefit profile:

None

Other reasons for considering the risks not important:

None

### SVII.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

| **Important identified risk** | **Cytokine release syndrome (CRS)** |
|---|---|
| Risk-benefit impact | CRS is a disorder characterised by fever, tachypnea, headache, tachycardia, hypotension, rash, and/or hypoxia. The mechanism of action for any T-cell engaging immunotherapy, such as odronextamab, results in non physiologic T-cell activation with cytokine release. The incidence and severity of CRS might be related to both tumour type and tumour burden.<br><br>In patients with FL and DLBCL from Study 1333 and Study 1625, CRS events with the recommended step-up regimen (0.7/4/20 mg) were predominately low grade, highest grade was grade 1 in 39.6% (46.8% in patients with FL, 34.7% in patients with DLBCL), with grade 2 in 13.7% (10.1% in patients with FL, 16.1% in patients with DLBCL) and grade 3 in 1.0% (1.3% in patients with FL, 0.8% in patients with DLBCL) of patients. No patients experienced grade 4 or grade 5 CRS events.<br><br>Additional details are provided in Part II: Module SVII.3. Detailed guidance for how to manage and mitigate this risk is provided in the SmPC and PI. A Patient Card is included as an additional risk minimisation measure to further mitigate the risk of CRS.<br><br>Overall, the risk-benefit balance is positive for odronextamab. |
| **Important identified risk** | **Serious Infections** |
| Risk-benefit impact | Infections are commonly observed in patients with B-cell lymphoma, especially in the setting of R/R disease, where patients have often been exposed to multiple prior lines of B-cell depleting therapies and other cytotoxic agents that have broad and long-term immunosuppressive effects. In addition, because the clinical programme for odronextamab spans the duration of the COVID-19 pandemic, most patients were at background risk of COVID-19 infection. Based on the MOA, treatment predictably results in pronounced B-cell depletion and hypogammaglobulinaemia in most patients. Marked depletion of B cells can increase the risk of severe infections, including risk of CMV, hepatitis B reactivation and upper respiratory tract infections.<br><br>Among 153 patients with R/R FL who received odronextamab, serious infections occurred in 67/153 (43.8%) patients, with grade 3 infections in 27.5% and grade 4 infections in 2.6% of patients. Infections that were fatal within 90 days of the last dose occurred in 8.5% (13/153) of patients, |

| | |
|---|---|
| | and of these infections, 61.5% (8/13) were due to COVID-19 infection. The most common grade 3 or greater serious infections (≥ 2%) were COVID-19 (9.2%), pneumonia (8.5%), COVID-19 pneumonia (7.2%), cytomegalovirus infection (3.3%), urinary tract infection (2.6%), sepsis (2.6%), and cytomegalovirus infection reactivation (2.0%).<br><br>Among 219 patients with R/R DLBCL who received odronextamab, serious infections occurred in 72/219 (32.9%) patients, with grade 3 infections in 24.2% and grade 4 infections in 0.9% of patients. Infections that were fatal within 90 days of the last dose occurred in 8.7% (19/219) of patients, and of these infections, 42.1% (8/19) were due to COVID-19 infection. The most common grade 3 or greater serious infections (≥2%) were pneumonia (9.6%), COVID-19 (6.4%), *Pneumocystis jirovecii* pneumonia (3.7%), sepsis (3.2%) and COVID-19 pneumonia (2.7%).<br><br>Additional details are provided in Part II: Module SVII.3. Additional details of risk minimisation measures for serious infections are included in the SmPC.<br><br>Overall, the risk-benefit balance is positive for odronextamab. |
| **Important identified risk** | **Neurologic toxicity including ICANS** |
| Risk-benefit impact | Neurologic toxicity has been observed with the use of T-cell engaging therapies (Maude, 2018) ( Topp, 2015). A subset of neurologic events, including confusion, delirium, and aphasia have been observed, often overlapping with CRS, and previously considered to be part of CRS (Lee, 2014). These symptoms are now considered to be a separate syndrome (ICANS), which can occur with or without CRS. The mechanism is not fully understood, and cytokines may be implicated in the pathophysiology (Lee, 2019b).<br><br>Overall, treatment-emergent events representing possible neurologic toxicity were reported in 154/372 (41.4%) patients in the FL+DLBCL Combined Pool, with grade 3 or 4 treatment-emergent events in 26 (7.0%) patients (10 [6.5%] patients with FL, 16 [7.3%] patients with DLBCL) and no grade 5 treatment-emergent events. By PT, the most common events occurring in ≥10 patients (all grades) were Headache, Dizziness, Anxiety, Confusional state, Encephalopathy, and Tremor. Most of these events (headache, dizziness, anxiety) are non-specific and common in the general and/or elderly population. A grade 2 event (PT) of ICANS was reported in only 1/372 (0.3%) patient.<br><br>Additional details are provided in Part II: Module SVII.3. Detailed guidance for how to manage and mitigate this risk is provided in the SmPC and PI. A Patient Card is included as an additional risk |

| | |
|---|---|
| | minimisation measure to further mitigate the risk of neurologic toxicity including ICANS.<br>Overall, the risk-benefit balance is positive for odronextamab. |
| **Important Potential Risks** | **Risk of overdose due to medication errors** |
| Risk-benefit impact | Potential events of overdose due to medication errors may occur with the administration of odronextamab. A total of 6 cases of overdose with odronextamab have been reported in patients with FL (6/153 [3.9%]) and 3 cases have been reported in patients with DLBCL (3/219 [1.4%]). The root cause for majority of these errors was mitigated with clarifications to the carton and vials.<br>Overall, the risk-benefit balance is positive for odronextamab. |
| **Missing information** | **Long-term safety** |
| | There are limited data available regarding safety with long-term use of odronextamab.<br>The long-term safety of odronextamab will be monitored through the ongoing R1979-ONC-1625 and R1979-HM-1333 studies, and from safety data from post-authorisation efficacy studies (R1979-HM-2299 and R1979-ONC-22102). |

## SVII.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

Not applicable.

## SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

The important identified and potential risks for odronextamab have been determined based on observation in preclinical toxicology or clinical studies with odronextamab, risks reported with T-cell engaging immunotherapies, as well as risks generally associated with monoclonal antibodies.

**Important Identified Risks:**

1. CRS
2. Serious infections
3. Neurologic toxicity including ICANS

**Important Potential Risks:**

1. Risk of overdose due to medication errors

**Missing Information:**

1. Long-term safety

MedDRA version 24.1 was used to classify the clinical trial adverse event information that is summarised in this section.

### SVII.3.1 Presentation of Important Identified Risks and Important Potential Risks

**Important Identified Risk: CRS**

Potential mechanisms:

Odronextamab is a human bsAb which targets the CD3 receptor on T-cells and CD20 on B-cells and subsequently promotes T-cell activation and causes cytokine release (such as IL-6), which may result in CRS.

Evidence source(s) and strength of evidence:

Cytokine release syndrome is a known class effect associated with bispecific antibodies that bind to CD3. Cytokine release syndrome has been reported in patients with FL and DLBCL treated with odronextamab. Based on the strength of evidence from the clinical trial data and scientific literature, CRS is considered an important identified risk for odronextamab. Information regarding this adverse reaction is described in the odronextamab SmPC.

Characterisation of the risk:

CRS is a disorder characterised by fever, tachypnea, headache, tachycardia, hypotension, and/or hypoxia. Transient elevation of liver enzymes has been observed in patients experiencing CRS.

CRS was graded according to the ASTCT criteria adapted from (Lee, 2019) for all patients treated with the recommended step-up regimen. CRS events in a few patients enrolled earlier in both the 1625 and 1333 studies were graded according to the criteria adapted from (Lee, 2014).

CRS information presented below is based on the 0.7/4/20 mg step-up regimen modified during the course of the studies to further reduce the rates of grade 3 or higher CRS events. This is the recommended step-up regimen that is described in the SmPC recommended dose section. During development, the modification in the step-up regimen was successful in mitigating the risk of CRS in patients with FL grade 1-3a and DLBCL. The CRS events reported in 0.7/4/20 mg step-up regimen were predominantly grade 1 with a low incidence of grade 2 and very low incidence of grade 3 CRS events. No grade 4 or 5 CRS events have been reported. The proposed product labelling recommends this same 0.7/4/20 mg step-up regimen with its associated premedication and guidance for intervention.

*FL*

Overall (as of the data cut-off date of 20 Oct 2023 for Study 1625 and 19 Sep 2023 for Study 1333), 46/79 (58.2%) patients who received the 0.7/4/20/80 mg step-up regimen experienced an event of CRS. Most CRS events were reported prior to the second full dose (44/46 patients) and most CRS events were grade 1 (37/79 [46.8%] patients). By the second full dose and beyond,

10/69 (14.5%) patients experienced CRS events, most (9/69 [13.0%]) were grade 1 and 1/69 (1.4%) was grade 2. Overall, there was 1 grade 3 event (1/79 [1.3%]) and no grade 4 or 5 CRS events. No patients discontinued treatment due to CRS and all patients who experienced CRS were able to resume treatment. The median time to onset of CRS from the end of infusion across all doses in the recommended dosage regimen was 26.30 hours (range: 0.7 hours to 159.0 hours).

The most common presenting signs and symptoms of CRS in patients with FL were Pyrexia (44/79 [55.7%] patients), Hypotension (9/79 [11.4%] patients), Tachycardia (4/79 [5.1%]), Hypoxia (4/79 [5.1%]), and Chills (3/79 [3.8%]).

*DLBCL*

Overall (as of the data cut-off date of 20 Oct 2023 for Study 1625 and 19 Sep 2023 for Study 1333), 61/118 (51.7%) patients who received the 0.7/4/20/160 mg step-up regimen experienced an event of CRS. Most CRS events were reported prior to the second full dose (59/118 [50.0%] patients). Most CRS events were grade 1 (41/118 [34.7%] patients). By the second full dose and beyond, 7/88 (8.0%) patients experienced CRS events, most were grade 1 with 1 grade 2 and 1 grade 3 event each (the grade 3 event reported was confounded by pancreatitis). There were no grade 4 or 5 events. One patient discontinued treatment due to CRS. The median time to onset of CRS from the end of infusion across all doses in the recommended dosage regimen was 18.00 hours (range: -3.4 hours to 221.0 hours).

The most common presenting signs and symptoms of CRS occurring in ≥5% of patients with DLBCL were Pyrexia (57/118 [48.3%] patients), Hypotension (13/118 [11.0%] patients), and Hypoxia (9/118 [7.6%] patients).

*FL + DLBCL Pool*

Overall, 107/197 (54.3%) patients (FL and DLBCL) who received the 0.7/4/20/160 mg step-up regimen experienced an event of CRS. Most CRS events were reported prior to the second full dose (103/197 [52.3%]). Most CRS events were grade 1 (78/197 [39.6%] patients) and grade 2 (27/197 [13.7%] patients) with 2/197 (1.0%) patients experiencing grade 3 CRS (in one patient grade 3 event reported was confounded by pancreatitis). There were no grade 4 or 5 events. One (0.5%) patient discontinued treatment due to CRS. Among the patients with time to onset data available, the median time to onset of CRS from the end of infusion was 19.83 hours (range: -3.4 to 221.0) for patients.

The most common presenting signs and symptoms of CRS occurring in ≥5% of patients with FL and DLBCL were Pyrexia (101/197 [51.3%] patients), Hypotension (22/197 [11.2%] patients), and Hypoxia (13/197 [6.6%]).

Risk factors and risk groups:

The incidence and severity of CRS might be related to both tumour type and tumour burden. Cross-linking of TCRs is dependent on binding to CD20; the greater the amount of CD20 binding (eg, due to tumour-load), the greater the opportunity for cross-linking of TCRs by CD3 (Yáñez, 2020).

Preventability:

Measures in place for prevention of CRS occurrence include infusing at a low rate, step-up regimen administered as split doses, and the use of premedication. Additional measures for early detection and management include monitoring for signs and symptoms (including guidance to patients on

the signs and symptoms with guidance on when to seek support), and depending on severity, potential actions include withholding odronextamab, infusing at a lowered rate, increasing frequency of monitoring, considering hospitalisation, supportive therapy and/or intensive care, and permanently discontinuing odronextamab. During the step-up dosing and the first full dose, patients will be instructed to remain in proximity to the qualified healthcare facility for at least 24 hours following each dose.

Guidance for how to monitor, manage, and mitigate this risk is provided in the SmPC. Annex 6 of the RMP provides details of additional risk minimisation measures (ie, patient card) for patients treated with odronextamab. The patient card that reminds patients about key symptoms that need to be reported immediately to a physician/nurse will be provided to patients who will be instructed on the need to carry this card at all times.

With the availability of multiple approved T-cell engaging therapies (CAR-T and bispecifics), healthcare providers experienced in treating R/R lymphoma are already familiar with CRS and are well-equipped to safely manage patients with outpatient monitoring.

Impact on the risk-benefit balance of the product:

CRS is a known class effect associated with bispecific T-cell engagers, including bispecific antibodies that bind to CD3.

While CRS may be life-threatening or fatal, the majority of CRS events with odronextamab from the clinical trials were grade 1 or grade 2. Most CRS events were grade 1 (78/197 [39.6%] patients) and grade 2 (27/197 [13.7%] patients) with 2/197 (1.0%) patients experiencing grade 3 CRS. 99% of CRS events resolved, and the median duration of CRS was 2 days (range: 1 to 10 days). CRS events occurred predominantly in Cycle 1. All events of CRS were effectively managed with available treatments recommended for management of CRS and there were no grade 4 or 5 events.

Overall, the risk-benefit balance is positive for odronextamab considering that the proposed indications are life-threatening, the demonstrated efficacy for patients, and the low grade severity of CRS observed in the clinical trials at the recommended step-up regimen.

Public health impact:

Odronextamab will be administered in a controlled clinical setting by healthcare professionals. No public health impact is anticipated.

**Important Identified Risk: Serious Infections**

Potential mechanisms:

Infections are commonly observed in patients with B-cell lymphoma, especially in the setting of R/R disease, where patients have often been exposed to multiple prior lines of B-cell depleting therapies and other cytotoxic agents that have broad and long-term immunosuppressive effects. However, and in addition, due to the odronextamab mechanism of action, treatment predictably results in pronounced B-cell depletion and hypogammaglobulinaemia in most patients. This is further compounded by the existing B-cell dysfunction due to the underlying malignancy. Marked depletion of B-cells can increase the risk of severe infections, including risk of CMV and hepatitis B reactivation and upper respiratory tract infections.

Evidence source(s) and strength of evidence:

Based on the strength of evidence from the clinical trial data and scientific literature, serious infections are considered an important identified risk for odronextamab. Information regarding this adverse reaction is described in the odronextamab SmPC.

Characterisation of the risk:

Infections are based on events in the SOC of Infections and infestations. Odronextamab development coincided with the height of the COVID-19 pandemic, and incidence of infections presented herein should be considered in that context.

*FL*

Serious infections occurred in 67/153 (43.8%) patients, with grade 3 infections in 27.5% and grade 4 infections in 2.6% of patients. Infection2s that were fatal within 90 days of the last dose occurred in 8.5% (13/153) of patients, and of these infections, 61.5% (8/13) were due to COVID-19 infection. The most common grade ≥3 serious infections (≥2%) were COVID-19 (9.2%), Pneumonia (8.5%), COVID-19 pneumonia (7.2%), Cytomegalovirus infection (3.3%), Urinary tract infection (2.6%), Sepsis (2.6%), and Cytomegalovirus infection reactivation (2.0%).

*DLBCL*

Serious infections occurred in 72/219 (32.9%) patients, with grade 3 infections in 24.2% and grade 4 infections in 0.9% of patients. Infections that were fatal within 90 days of the last dose occurred in 8.7% (19/219) of patients, and of these infections, 42.1% (8/19) were due to COVID-19 infection. The most common grade ≥3 serious infections (≥2%) were Pneumonia (9.6%), COVID-19 (6.4%), *Pneumocystis jirovecii* pneumonia (3.7%), Sepsis (3.2%), and COVID-19 pneumonia (2.7%).

*FL + DLBCL Pool*

Overall, 248/372 (66.7%) patients experienced infections; the incidence of ≥grade 3 infections was 138/372 (37.1%). The most common infections by PT were COVID-19, Pneumonia, Urinary tract infection, and Upper respiratory tract infection. Overall, 29/372 (7.8%) patients had infections resulting in treatment discontinuation. By PT, infections resulting in treatment discontinuation in ≥2 patients were COVID-19 (9/372 [2.4%] patients), Pneumonia (5/372 [1.3%] patients), COVID-19 pneumonia (2/372 [0.5%] patients), *Pneumocystis jirovecii* pneumonia (2/372 [0.5%] patients), and Pulmonary tuberculosis (2/372 [0.5%] patients).

Risk factors and risk groups:

Patients with FL and DLBCL are susceptible to infections due to immunosuppression related to their underlying disease. The receipt of prior lines of lymphodepleting therapy further increases their risk for infections. Pronounced B-cell depletion and hypogammaglobulinaemia could result in increased susceptibility to infection including reactivation of latent hepatitis B infection. In addition, patients with haematological malignancies who have COVID-19 have worse mortality outcomes than the general population with COVID-19 (Passamonti, 2020) (Vijenthira, 2020). Analysis of real-world data and literature review suggested that the risk of severe and fatal infections, including COVID-19 infections, is high in heavily pre-treated FL and DLBCL, patients with relapsed/refractory disease. Overall infections rates in the real-world analysis were comparable or higher with the results observed in Studies 1625 and 1333.

Preventability:

Monitor patients for signs and symptoms of infection prior to and during treatment with odronextamab and treat appropriately. Odronextamab should not be administered in the presence of active infection. Caution should be exercised when considering the use of odronextamab in patients with a history of recurring or chronic infections. Administer prophylactic antimicrobials as appropriate.

Infection risk is adequately managed by prophylaxis, as appropriate, and routine clinical monitoring and treatment. Prophylactic treatment is recommended for patients with a history of herpes virus infections and cytomegalovirus infections. Antiviral treatment is recommended for patients with positive hepatitis B surface antigen, hepatitis B core antibody and/or measurable viral load. IVIG should be considered per guidelines. In the event of febrile neutropenia, patients should be evaluated for infection and managed with antibiotics, fluids, and other supportive care, according to local guidelines. Detailed guidance for how to manage and mitigate the risk of serious infections is provided in the SmPC.

Due to potential hypogammaglobulinaemia, in accordance with local institutional guidelines, immunoglobulin levels should be monitored and hypogammaglobulinaemia should be treated.

Impact on the risk-benefit balance of the product:

Odronextamab is expected to reduce B-cells, which may lead to hypogammaglobulinaemia, resulting in an increased risk of infections. The incidence of serious infection in the FL and DLBCL populations is expected to be high due to the underlying disease and the prior receipt of lymphodepleting therapies.

In R/R lymphoma populations, infection risk is adequately managed by prophylaxis, as appropriate, and routine clinical monitoring and treatment.

Overall, the risk-benefit balance is positive for odronextamab considering the severity of the proposed indications, the risk minimisation measures implemented, and the demonstrated efficacy.

Public health impact:

Odronextamab will be administered in a controlled clinical setting by healthcare professionals. No public health impact is anticipated.

**Important Identified Risk: Neurologic toxicity including ICANS**

Potential mechanisms:

Neurologic toxicity has been reported with other T-cell engagers. The mechanism is not fully understood, and cytokines may be implicated in the pathophysiology.

Evidence source(s) and strength of evidence:

Neurologic toxicity has been observed with the use of T-cell engaging therapies. A subset of neurologic events, including confusion, delirium, and aphasia have been observed, often overlapping with CRS, and previously considered to be part of CRS. These symptoms are now considered to be a separate syndrome (ICANS), which can occur with or without CRS. Based on the strength of evidence from the clinical trial data and scientific literature, neurologic toxicity including ICANS is considered an important identified risk for odronextamab. Information regarding this risk is described in the odronextamab SmPC.

Characterisation of the risk:

The risk of neurologic toxicity including ICANS was characterised by all MedDRA PTs included within the SOCs of Nervous System Disorders and/or Psychiatric Disorders, excluding the High Level Group Terms of Peripheral Neuropathies and Sleep Disorders and disturbances. A case definition of ICANS was not provided in studies 1333 and 1625, and several different terms were reported for neurologic events that sometimes occur as signs or symptoms of ICANS when they occur following treatment with a T-cell engaging therapy (Lee, 2019b).

*FL*

Events occurred in 68/153 (44.4%) patients, with grade 3 events in 10/153 (6.5%) of patients and no grade 4 or 5 events. The grade 3 events were Syncope (3.3%); and Tremor, Cerebrovascular accident, Neurotoxicity, Frontal lobe epilepsy, Transient ischaemic attack, and Monoparesis in one patient each (0.7%). ICANS occurred in 1/153 (0.7%) patient (grade 2).

*DLBCL*

Events occurred in 86/219 (39.3%) patients, with grade 3 or 4 events in 16/219 (7.3%) of patients and no grade 5 events. The most common ≥grade 3 events (2 patients or more) were Encephalopathy (3.2%) and Syncope, Cognitive disorder, and Confusional state (0.9%, 2 patients each). The grade 4 events reported in 3 patients with DLBCL were Encephalopathy, Cerebral Hemorrhage, and Brain edema. No patients experienced the MedDRA PT of ICANS.

*FL + DLBCL Pool*

Overall, 154/372 (41.4%) patients experienced events; the incidence of patients with grade ≥3 events was 26/372 (7.0%). The most common events by PT (≥3%) were Headache, Dizziness, Encephalopathy, Anxiety, and Confusional state. Overall, 8/372 (2.2%) patients had events resulting in treatment discontinuation; Encephalopathy in 3/372 (0.8%) patients and Epilepsy, Frontal lobe epilepsy, Cerebral haemorrhage, Aphasia, Depressive symptom, and Tremor in 1/372 (0.3%) patient each. ICANS occurred in 1/372 (0.3%) patient (grade 2).

Risk factors and risk groups:

Risk factors have not been fully identified. Patients with CNS disorders may be at higher risk for neurological AEs.

Preventability:

Odronextamab must only be administered under the supervision of a healthcare professional experienced in the diagnosis and treatment of cancer patients and who has access to appropriate medical support to manage reactions such as neurologic toxicities. With the availability of multiple approved T-cell engaging therapies (CAR-T and bispecifics), healthcare providers experienced in treating R/R lymphoma are already familiar with ICANS and are well-equipped to identify and safely manage patients with neurologic toxicity.

Guidance for how to manage and mitigate this risk is provided in the SmPC. Annex 6 of the RMP provides details of additional risk minimisation measures (ie, patient card) for patients treated with odronextamab. The patient card reminds patients about key symptoms that need to be reported immediately to a physician/nurse and will be provided to patients who will be instructed on the need to carry this card at all times.

Impact on the risk-benefit balance of the product:

The risk of neurologic toxicity including ICANS is adequately managed by clinical monitoring and treatment. Detailed guidance for how to manage and mitigate this risk is provided in the SmPC.

Overall, the risk-benefit balance is positive for odronextamab considering the severity of the proposed indications, the risk minimisation measures implemented, and the demonstrated efficacy.

Public health impact:

Odronextamab will be administered in a controlled clinical setting by healthcare professionals. No public health impact is anticipated.

**Important Potential Risk: Risk of overdose due to medication errors**

Potential Mechanisms

Potential medication errors leading to overdose could occur in the prescribing, preparation, dispensing, and administration of odronextamab.

Evidence Source(s) and Strength of Evidence:

Odronextamab clinical trials.

Characterisation of the Risk

Potential events of overdose due to medication errors may occur with the administration of odronextamab.

A total of 9 cases of overdose with odronextamab have been reported in patients with FL+DLBCL (9/372 [2.4%] patients).

Events of overdose were infrequent and due to medication errors. Events predominantly occurred during the step-up regimen (5/9 overdoses). Risk minimisation measures were implemented during clinical development to reduce the occurrence of overdoses. Four overdoses occurred during step-up dosing before these measures were implemented. Following the implementation of these measures, in 197 patients treated with the revised regimen, overdose was reported in 1 patient and this event was due to human error and not due to the same causes noted in earlier events of overdose and was not associated with any significant adverse events.

Risk Factors and Risk Groups:

No risk factors and no risk groups were identified in odronextamab clinical trials.

Preventability:

To mitigate the risk of overdose due to medication errors with odronextamab, comprehensive instructions for dosing schedule, dilution, preparation, and administration procedures are provided in the SmPC. The concentrations are clearly written on the carton and vial labels in different colour for each strength. The 3 vials will be distinguished by the clear labelling on the vials and further supported by the different colour of the vial caps and vial sizes for the 2 mg, 80 mg, and 320 mg presentations.

The proposed odronextamab label and commercial presentations are expected to adequately mitigate potential occurrences of overdose.

Impact on the Risk-Benefit Balance of the Product:

The causes for these overdoses due to medication errors are not related to the product quality and usually can be avoided if the approved prescribing instruction for dilution, preparation, and administration is strictly followed. The benefit-risk balance remains positive.

Public Health Impact:

Odronextamab will be administered in a controlled clinical setting by healthcare professionals. No public health impact is anticipated.

### SVII.3.2 Presentation of the Missing Information

| | |
|---|---|
| **Missing information** | Long-term safety data |
| **Evidence Source** | Limited data are available on long-term exposure.<br>The long-term safety of odronextamab will be monitored through the ongoing R1979-ONC-1625 and R1979-HM-1333 studies, and from safety data from post-authorisation efficacy studies (R1979-HM-2299 and R1979-ONC-22102). |
| **Population in need of further characterisation** | Not currently defined per current evidence, but long-term safety data may be available at a later date |

# PART II: MODULE SVIII SUMMARY OF THE SAFETY CONCERNS

### Table Part II: Module SVIII.1: Summary of Safety Concerns

| **Summary of safety concerns** | |
|---|---|
| Important identified risks | CRS<br>Serious infections<br>Neurologic toxicity including ICANS |
| Important potential risks | Risk of overdose due to medication errors |
| Missing information | Long-term safety data |

# PART III PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

## III.1 Routine Pharmacovigilance Activities

**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection.**

**Specific adverse reaction follow-up questionnaires for safety concerns:**

Not applicable

**Other forms of routine pharmacovigilance activities for safety concerns:**

Not applicable.

## III.2 Additional Pharmacovigilance Activities

No additional pharmacovigilance activities are planned for this product.

## III.3 Summary Table of Additional Pharmacovigilance Activities

No additional pharmacovigilance activities are planned for this product.

# Part IV PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

| Study Status | Objectives | Efficacy Uncertainties Addressed | Milestones | Due Dates |
|---|---|---|---|---|
| **Efficacy studies which are conditions of the marketing authorisation** | | | | |
| Not applicable | | | | |

| Study Status | Objectives | Efficacy Uncertainties Addressed | Milestones | Due Dates |
|---|---|---|---|---|
| **Efficacy studies which are Specific Obligations in the context of a conditional marketing authorisation or marketing authorisation under exceptional circumstances** | | | | |
| R1979-HM-2299 (OLYMPIA-4):<br>A phase 3, randomised, open-label study evaluating the efficacy and safety of odronextamab versus Standard of Care therapy in participants with R/R aggressive B-cell non-Hodgkin Lymphoma<br><br>Ongoing | To compare the efficacy, as defined by event-free survival, in participants treated with odronextamab versus participants treated with Standard of Care | To further confirm clinical efficacy and safety of odronextamab in R/R DLBCL<br><br>Safety concerns addressed:<br>CRS;<br>Serious Infections;<br>Neurologic toxicity including ICANS;<br>Long term safety | Protocol<br><br>Interim reports<br><br>Final study report | 31 Jul 2023<br><br>None<br><br>Nov 2028 |
| R1979-ONC-22102 (OLYMPIA-5):<br>A phase 3, open-label, randomised study to compare the efficacy and safety of odronextamab in combination with lenalidomide versus rituximab in combination with lenalidomide in R/R participants with FL and MZL.<br><br>Ongoing | Part 1 (safety run - in) primary objectives are to assess the safety, tolerability, and DLTs of odronextamab in combination with lenalidomide in participants with R/R FL and MZL<br>Part 2 primary objective is to compare the efficacy of odronextamab in combination with lenalidomide versus R2 in participants with R/R FL and subsequently in participants with R/R indolent lymphoma (combined R/R | To further confirm clinical efficacy and safety of odronextamab in R/R FL<br><br>Safety concerns addressed:<br>CRS;<br>Serious Infections:<br>Neurologic toxicity including ICANS;<br>Long term Safety | Protocol<br><br>Interim reports<br><br>Final study report for FL | 31 Jul 2023<br><br>To be confirmed<br><br>Sep 2031 |

1.8.2 Risk Management Plan

| Study Status | Objectives | Efficacy Uncertainties Addressed | Milestones | Due Dates |
|---|---|---|---|---|
| | FL and MZL) as measured by PFS per independent central review. | | | |

# PART V RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

## V.1 Routine Risk Minimisation Measures

**Table Part V.1: Description of Routine Risk Minimisation Measures by Safety Concern**

| **Safety concern** | Routine risk minimisation activities |
|---|---|
| Cytokine release syndrome | **Routine risk communication:**<br>SmPC Section 4.2, 4.4, and 4.8<br>PL Section 2 and 4<br>**Routine risk minimisation activities recommending specific clinical measures to address the risk:**<br>SmPC Section 4.2, 4.4, and 4.7<br>PL Section 2, 3 and 4<br>• Instructions that odronextamab must only be administered under the supervision of a healthcare professional experienced in the diagnosis and treatment of cancer patients and who has access to appropriate medical support to manage severe reactions as associated with CRS are provided in SmPC Section 4.2.<br>• Instructions that at least 1 dose of tocilizumab for use in the event of CRS should be available prior to odronextamab administration for Cycle 1 and that access to an additional dose of tocilizumab within 8 hours of use of the previous tocilizumab dose should be available are provided in SmPC Section 4.2.<br>• Instructions that premedications (corticosteroid, antihistamine, antipyretics) must be administered for each dose in Cycle 1 and Cycle 2, Days 1 and 8, and post-medications for Cycle 1, Days 3,10, and 17 and Cycle 2, Day 2 to reduce the risk of CRS are provided in SmPC Sections 4.2 and 4.4.<br>• Instructions that patients be monitored for signs and symptoms of CRS during and after administration of odronextamab and remain within proximity of a qualified healthcare facility for at least 24 hours after administration of each dose within the step-up dosing regimen and the first full dose.<br>• Instructions that if CRS of grade 1 to 3 occurs, premedications should be administered prior to the next dose of odronextamab and patients monitored more frequently. |

| **Safety concern** | Routine risk minimisation activities |
|---|---|
| | • Use of step-up dosing (0.7/4/20mg) to reduce the incidence and severity of CRS is described in SmPC Sections 4.2 and 4.4.<br>• Recommendation to withhold odronextamab until any grade 1, grade 2, or grade 3 CRS event resolves in provided in SmPC Sections 4.2 and 4.4.<br>• Recommendation to permanently discontinue odronextamab for any grade 4 CRS event is provided in SmPC Sections 4.2 and 4.4.<br>• Instruction to administer dexamethasone and/or tocilizumab for grade 2, 3, or 4 CRS events and consider dexamethasone and/or tocilizumab for grade 1 CRS events is provided in SmPC Section 4.2.<br>• Instructions to immediately evaluate patients for hospitalisation and administer supportive care at the first signs of CRS is provided in Sections 4.2 and 4.4.<br>• Instructions that following grade 3 CRS when clinical symptoms have resolved patients should be hospitalised for the next dose of odronextamab and detailed dosing instructions are provided in SmPC Section 4.2.<br>• Recommendations that patients should be counselled to seek immediate medical attention should signs or symptoms of CRS occur at any time are provided in SmPC Section 4.4.<br>• Instructions to evaluate patients who experience CRS and advise not to drive or refrain from operating heavy or potentially dangerous machinery until resolution is provided in SmPC Section 4.4 and 4.7 and PL section 2.<br>• Instructions for patients to carry Patient Card at all times and show it to all of their healthcare providers is provided in SmPC Section 4.4 and PL Introductory text.<br>• Patients should get medical help right away if signs of CRS occur, as described in PL Sections 2, 3 and 4.<br>**Other routine risk minimisation measures beyond the Product Information:**<br>Legal status: Odronextamab is subject to restricted medical prescription, and treatment must be initiated and supervised by healthcare professionals experienced in the treatment of cancer. |
| Serious Infections | **Routine risk communication:**<br>SmPC Section 4.2, 4.4, and 4.8<br>PL Section 2 and 4 |

| **Safety concern** | Routine risk minimisation activities |
|---|---|
| | **Routine risk minimisation activities recommending specific clinical measures to address the risk:**<br><br>SmPC Section 4.2 and 4.4<br><br>PL Section 2 and 4<br><br>• Recommendation that odronextamab should not be administered in patients with active infections is provided in SmPC Sections 4.2 and 4.4.<br><br>• Recommendations to administer the following infection prophylactic treatments as appropriate is outlined in SmPC Sections 4.2 and 4.4: prophylactic antimicrobials, prophylaxis for *Pneumocystis jirovecii* pneumonia, prophylactic treatment in patients with a history of herpes virus infections or CMV infections.<br><br>• Recommendation to monitor patients for signs and symptoms of infection prior to and during treatment with Odronextamab and treat appropriately is provided in SmPC Section 4.4.<br><br>• Instruction that, in the event of febrile neutropenia, patients should be evaluated for infection and managed appropriately, according to local guidelines is provided in SmPC Section 4.4.<br><br>• Recommendations for antiviral treatment for patients with positive Hepatitis B surface antigen, hepatitis B core antibody, and/or measurable viral load is provided in SmPC Section 4.4.<br><br>• Recommendation to consider IVIG is provided in SmPC Section 4.4.<br><br>• Recommendation to withhold odronextamab in patients with active infection until the infection resolves is provided in SmPC Sections 4.2 and 4.4.<br><br>• Recommendation to consider permanent discontinuation of odronextamab in patients with grade 4 infections is provided in SmPC Sections 4.2 and 4.4.<br><br>• Patients should tell their doctor if they have any signs of infection, as described in PL Sections 2 and 4.<br><br>**Other routine risk minimisation measures beyond the Product Information:**<br>Legal status: Odronextamab is subject to restricted medical prescription, and treatment must be initiated and supervised by healthcare professionals experienced in the treatment of cancer. |
| Neurologic toxicity including ICANS | **Routine risk communication:** |

| **Safety concern** | Routine risk minimisation activities |
|---|---|
| | SmPC Section 4.2, 4.4 and 4.8<br><br>PL Section 2 and 4<br><br>**Routine risk minimisation activities recommending specific clinical measures to address the risk:**<br><br>SmPC Section 4.2 and 4.4<br><br>PL Section 2 and 4<br><br>• Instructions to provide supportive therapy and consider neurologic evaluation is provided in SmPC Section 4.2 and 4.4<br><br>• Recommendation to withhold odronextamab for grade 1 or grade 2 ICANS until resolution is provided in SmPC Sections 4.2 and 4.4.<br><br>• Recommendation to permanently discontinue odronextamab for grade 3 or 4 ICANS is provided in the SmPC Sections 4.2 and 4.4.<br><br>• Recommendation to withhold odronextamab until grade 2 or grade 3 neurologic toxicity event improve to grade 1 or baseline is provided in SmPC Sections 4.2 and 4.4<br><br>• Recommendation to permanently discontinue odronextamab for grade 4 neurologic events is provided in SmPC Sections 4.2 and 4.4<br><br>• Instructions for patients to carry Patient Card at all times, and show it to all of their healthcare providers is provided in SmPC Section 4.4 and PL introductory text.<br><br>**Other routine risk minimisation measures beyond the Product Information:**<br><br>Legal status: Odronextamab is subject to restricted medical prescription, and treatment must be initiated and supervised by healthcare professionals experienced in the treatment of cancer. |
| Risk of overdose due to medication errors | **Routine risk communication:**<br><br>SmPC Section 4.2 and 4.9<br><br>**Routine risk minimisation activities recommending specific clinical measures to address the risk:**<br><br>• In case of overdose, recommendation to closely monitor for signs and symptoms of adverse reactions, and appropriate symptomatic treatment instituted is included in SmPC Section 4.9.<br><br>**Other routine risk minimisation measures beyond the Product Information:** |

| | |
|---|---|
| **Safety concern** | Routine risk minimisation activities |
| | • Prescription-only medicine |
| Missing information:<br>Long-term safety data | No risk minimisation measures |

## V.2 Additional Risk Minimisation Measures

| | |
|---|---|
| **Additional Risk Minimisation Activity 1**<br>Patient Card | |
| **Important Identified Risk:** Cytokine Release Syndrome | |
| **Objective(s):** | To minimise the risk of CRS by ensuring that patients are aware of the symptoms and know when to contact a healthcare professional |
| **Rationale for the additional risk minimisation activity:** | CRS can be serious if not detected and managed early. The additional risk minimisation activity is to facilitate early detection of CRS to ensure prompt medical intervention. |
| **Target audience and planned distribution path:** | All patients who are receiving treatment with odronextamab.<br>Patients will be given the Patient Card and instructed on the need to carry this card at all times and to show it to a physician/nurse at all times whenever they are treated by a medical professional. |
| **Plans to evaluate the effectiveness of the interventions and criteria for success:** | Effectiveness of the risk minimisation activity will be assessed using routine pharmacovigilance activities, the results of which will be communicated in the PSUR. Criteria for effectiveness will be based on observing stable reporting rates and severity of CRS, as well as targeted analysis of post marketing information received. |
| **Important Identified Risk:** Neurologic toxicity including ICANS | |
| **Objective(s):** | To minimise the risk of neurologic toxicity including ICANS by ensuring that patients are aware of the symptoms and know when to contact a healthcare professional |
| **Rationale for the additional risk minimisation activity:** | Neurologic toxicity including ICANS can be serious if not detected and managed early. The additional risk minimisation activity is to facilitate early detection of neurologic toxicity including ICANS to ensure prompt medical intervention. |

| | |
|---|---|
| **Target audience and planned distribution path:** | All patients who are receiving treatment with odronextamab.<br>Patients will be given the Patient Card and instructed on the need to carry this card at all times and to show it to a physician/nurse at all times whenever they are treated by a medical professional. |
| **Plans to evaluate the effectiveness of the interventions and criteria for success:** | Effectiveness of the risk minimisation activity will be assessed using routine pharmacovigilance activities, the results of which will be communicated in the PSUR. Criteria for effectiveness will be based on observing stable reporting rates and severity of neurologic toxicity including ICANS, as well as targeted analysis of post marketing information received. |

## V.3 Summary of Risk Minimisation Measures

**Table Part V.2: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern**

| Safety concern | Risk minimisation measures | Pharmacovigilance activities |
|---|---|---|
| Cytokine release syndrome | **Routine risk communication:**<br>SmPC Section 4.2, 4.4, and 4.8<br>PL Section 2 and 4<br>**Routine risk minimisation activities recommending specific clinical measures to address the risk:**<br>SmPC Section 4.2, 4.4, and 4.7<br>PL Section 2, 3 and 4<br>**Other routine risk minimisation measures beyond the Product Information:**<br>Legal status: Odronextamab is subject to restricted medical prescription, and treatment must be initiated and supervised by healthcare professionals experienced in the treatment of cancer.<br>**Additional risk minimisation measures:**<br>Patient Card | Routine pharmacovigilance |
| Serious Infections | **Routine risk communication:**<br>SmPC Section 4.2, 4.4, and 4.8 | Routine pharmacovigilance |

| Safety concern | Risk minimisation measures | Pharmacovigilance activities |
|---|---|---|
| | PL Section 2 and 4<br>**Routine risk minimisation activities recommending specific clinical measures to address the risk:**<br>SmPC Section 4.2 and 4.4<br>PL Section 2 and 4<br>**Other routine risk minimisation measures beyond the Product Information:**<br>Legal status: Odronextamab is subject to restricted medical prescription, and treatment must be initiated and supervised by healthcare professionals experienced in the treatment of cancer.<br>**Additional risk minimisation measures:**<br>None | |
| Neurologic toxicity including ICANS | **Routine risk communication:**<br>SmPC Section 4.2, 4.4 and 4.8<br>PL Section 2 and 4<br>**Routine risk minimisation activities recommending specific clinical measures to address the risk:**<br>SmPC Section 4.2 and 4.4<br>PL Section 2 and 4<br>**Other routine risk minimisation measures beyond the Product Information:**<br>Legal status: Odronextamab is subject to restricted medical prescription, and treatment must be initiated and supervised by healthcare professionals experienced in the treatment of cancer.<br>**Additional risk minimisation measures:**<br>Patient Card | Routine pharmacovigilance |
| Risk of overdose due to medication errors | **Routine risk communication:**<br>SmPC Section 4.2 and 4.9<br>**Other routine risk minimisation measures beyond the Product Information:**<br>Prescription-only medicine | Routine pharmacovigilance |

| Safety concern | Risk minimisation measures | Pharmacovigilance activities |
|---|---|---|
| Missing information: Long-term safety data | No risk minimisation measures | Routine pharmacovigilance |

# PART VI SUMMARY OF THE RISK MANAGEMENT PLAN

This is a summary of the RMP for odronextamab. The RMP details important risks of odronextamab, how these risks can be minimised, and how more information will be obtained about odronextamab risks and uncertainties (missing information).

Odronextamab SmPC and its package leaflet give essential information to healthcare professionals and patients on how odronextamab should be used.

This summary of the RMP for odronextamab should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the EPAR. To be adapted locally.

Important new concerns or changes to the current ones will be included in updates of the odronextamab RMP.

## I THE MEDICINE AND WHAT IT IS USED FOR

Odronextamab is indicated as monotherapy for the treatment of adult patients with:

**Follicular Lymphoma**

Odronextamab as monotherapy is indicated for the treatment of adult patients with relapsed or refractory FL after two or more lines of systemic therapy.

**Diffuse Large B-Cell Lymphoma**

Odronextamab as monotherapy is indicated for the treatment of adult patients with relapsed or refractory DLBCL, after two or more lines of systemic therapy.

Further information about the evaluation of odronextamab's benefits can be found in odronextamab's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage.

## II RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMISE OR FURTHER CHARACTERISE THE RISKS

Important risks of odronextamab, together with measures to minimise such risks and the proposed studies for learning more about odronextamab's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals
- Important advice on the medicine's packaging
- The authorised pack size—the amount of medicine in a pack—is chosen to ensure that the medicine is used correctly
- The medicine's legal status—the way a medicine is supplied to the patient (eg, with or without prescription)—can help to minimise its risks

Together, these measures constitute routine risk minimisation measures.

In the case of odronextamab, these measures are supplemented with additional risk minimisation measures mentioned under relevant important risks (Section II:II.A):

- Patient Card

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of odronextamab is not yet available, it is listed under 'missing information' (Section II:II.A).

## II.A List of Important Risks and Missing Information

Important risks of odronextamab are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of odronextamab. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

**Table II.1: Lists of Important Risks and Missing Information**

| **List of Important Risks and Missing Information** | |
|---|---|
| Important identified risks | CRS<br>Serious infections<br>Neurologic toxicity including ICANS |
| Important potential risks | Risk of overdose due to medication errors |
| Missing information | Long-term safety data |

## II.B Summary of Important Risks

| | |
|---|---|
| **Important identified risk: CRS** | |
| Evidence for linking the risk to the medicine | Cytokine release syndrome is a known class effect associated with bispecific antibodies that bind to CD3. Cytokine release syndrome has been reported in patients with FL and DLBCL treated with odronextamab. Based on the strength of evidence from the clinical trial data and scientific literature, CRS is considered an important identified risk for odronextamab. Information regarding this adverse reaction is described in the odronextamab SmPC. |
| Risk factors and risk groups | The incidence and severity of CRS might be related to both tumour type and tumour burden. Cross-linking of TCRs is dependent on binding to CD20; the greater the amount of CD20 binding (eg, due to tumour-load), the greater the opportunity for cross-linking of TCRs by CD3 (Yáñez, 2020). |
| Risk minimisation measures | **Routine risk communication:**<br>SmPC Section 4.2, 4.4 and 4.8<br>PL Section 2 and 4<br>**Routine risk minimisation activities recommending specific clinical measures to address the risk:**<br>SmPC Section 4.2, 4.4 and 4.7<br>PL Section 2, 3 and 4<br>**Other routine risk minimisation measures beyond the Product Information:**<br>Legal status: Odronextamab is subject to restricted medical prescription, and treatment must be initiated and supervised by healthcare professionals experienced in the treatment of cancer.<br>**Additional risk minimisation measures:**<br>Patient Card |
| **Important identified risk: Serious Infections** | |
| Evidence for linking the risk to the medicine | Based on the strength of evidence from the clinical trial data and scientific literature, serious infections are considered an important identified risk for odronextamab. Information regarding this adverse reaction is described in the odronextamab SmPC. |
| Risk factors and risk groups | Patients with FL and DLBCL are susceptible to infections due to immunosuppression related to their underlying disease. The receipt of prior lines of lymphodepleting therapy further increases their risk for infections. Pronounced B-cell depletion and hypogammaglobulinaemia could result in increased susceptibility to infection including reactivation of latent hepatitis B infection. In |

| | |
|---|---|
| | addition, patients with haematological malignancies who have COVID-19 have worse mortality outcomes than the general population with COVID-19. |
| Risk minimisation measures | **Routine risk communication:**<br>SmPC Section 4.2, 4.4 and 4.8<br>PL Section 2 and 4<br>**Routine risk minimisation activities recommending specific clinical measures to address the risk:**<br>SmPC Section 4.2 and 4.4<br>PL Section 2 and 4<br><br>**Other routine risk minimisation measures beyond the Product Information:**<br>Legal status: Odronextamab is subject to restricted medical prescription, and treatment must be initiated and supervised by healthcare professionals experienced in the treatment of cancer.<br>**Additional risk minimisation measures:**<br>None |
| **Important identified risk: Neurologic toxicity including ICANS** | |
| Evidence for linking the risk to the medicine | Based on the strength of evidence from the clinical trial data and scientific literature (Maude, 2018) ( Topp, 2015) , neurologic toxicity including ICANS is considered an important identified risk for odronextamab. |
| Risk factors and risk groups | Risk factors have not been fully identified. Patients with CNS disorders may be at higher risk for neurological AEs. |
| Risk minimisation measures | **Routine risk communication:**<br>SmPC Section 4.2, 4.4 and 4.8<br>PL Section 2 and 4<br>**Routine risk minimisation activities recommending specific clinical measures to address the risk:**<br>SmPC Section 4.2 and 4.4<br>PL Section 2 and 4<br>Other routine risk minimisation measures beyond the Product Information:<br>Legal status: Odronextamab is subject to restricted medical prescription, and treatment must be initiated and supervised by healthcare professionals experienced in the treatment of cancer.<br>**Additional risk minimisation measures:** |

| | |
|---|---|
| | Patient Card |
| **Important potential risk: Risk of overdose due to medication errors** | |
| Evidence for linking the risk to the medicine | Based on occurrences of events of medication errors in the clinical trial data, potential events of overdose due to medication errors may occur with administration of odronextamab. |
| Risk factors and risk groups | No risk factors and no risk groups were identified in odronextamab clinical trials. |
| Risk minimisation measures | **Routine risk communication:**<br>SmPC Section 4.2 and 4.9<br>**Other routine risk minimisation measures beyond the Product Information:**<br>Prescription-only medicine |
| **Missing information: Long-term Safety Data** | |
| Risk minimisation measures | No risk minimisation measures |
| Additional pharmacovigilance activities | None |

# II.C Post-Authorisation Development Plan

## II.C.1 Studies Which Are Conditions of the Marketing Authorisation

The following studies are conditions of the marketing authorisation:

**Study short name:** R1979-HM-2299 (OLYMPIA-4)

An ongoing, phase 3, randomised, open-label study evaluating the efficacy and safety of odronextamab versus standard of care therapy in participants with R/R aggressive B-cell non-Hodgkin Lymphoma

Purpose of the study: To compare the efficacy, as defined by event-free survival, and the safety in participants treated with odronextamab versus participants treated with Standard of Care

**Study short name:** R1979-ONC-22102 (OLYMPIA-5)

An ongoing, phase 3, open-label, randomised study to compare the efficacy and safety of odronextamab in combination with lenalidomide versus rituximab in combination with lenalidomide in R/R participants with FL and MZL.

- Purpose of the study: Part 1 (safety run -in) primary objectives are to assess the safety, tolerability, and DLTs of odronextamab in combination with lenalidomide in participants with R/R FL and MZL
- Part 2 primary objective is to compare the efficacy of odronextamab in combination with lenalidomide versus rituximab in combination with lenalidomide in participants

with R/R FL and subsequently in participants with R/R indolent lymphoma (combined R/R FL and MZL) as measured by PFS per independent central review.

### II.C.2 Other Studies in Post-Authorisation Development Plan

Not applicable.

# PART VII ANNEXES

## LIST OF ANNEXES

# ANNEX 4 SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Not applicable

# ANNEX 6 DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES (IF APPLICABLE)

Risk Minimisation Activity: Patient Educational Materials (Patient Card)

The MAA shall ensure that all physicians who are expected to prescribe odronextamab are provided with Patient Cards to give to patients treated with odronextamab.

The key elements of the patient educational material will contain the following:

- Description of the main signs and symptoms of cytokine release syndrome and neurologic toxicity including ICANS
- Guidance on when to notify their treating physician or seek immediate help if symptoms of cytokine release syndrome and/or neurological toxicity including ICANS occur
- Guidance to remain within close proximity of a qualified healthcare facility for at least 24 hours after administration of each dose within the Ordspono step-up dosing regimen and the first full dose
- The importance of carrying the Patient Card at all times and to show it at all medical visits to healthcare professionals in addition to the prescriber (eg, emergency healthcare professionals)
- Prompts to enter contact details of the physician

The Patient Card reminds patients about key symptoms that need to be reported immediately to a physician/nurse and to alert other physicians that the patient is treated with odronextamab.

Dreyling M, Ghielmini M, Rule S, Salles G, Ladetto M, Tonino SH, et al. Newly diagnosed and relapsed follicular lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology. 2021;32(3):298-308.

Ekberg S, E. Smedby K, Glimelius I, Nilsson-Ehle H, Goldkuhl C, Lewerin C, et al. Trends in the prevalence, incidence and survival of non-Hodgkin lymphoma subtypes during the 21st century – a Swedish lymphoma register study. British Journal of Haematology. 2020;189(6):1083-92.

Fallah M, Kharazmi E, Pukkala E, Tretli S, Olsen JH, Tryggvadottir L, et al. Familial risk of non-Hodgkin lymphoma by sex, relationship, age at diagnosis and histology: a joint study from five Nordic countries. Leukemia. 2016;30(2):373-8.

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