27 June 2024
EMA/518269/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Ordspono

International non-proprietary name: odronextamab

Procedure No. EMEA/H/C/006215/0000

Note

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

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List of abbreviations

ADA	Anti-drug antibody
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
AEX	Anion exchange
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate Aminotransferase
B-NHL	B-cell non-Hodgkin lymphoma
BBR	Bioburden reduction
BCL	B-cell lymphoma
BCL-2	B-cell lymphoma 2
BCL-6	B-cell lymphoma 6
BMI	Body mass index
BOR	Best overall response
BSE	Bovine spongiform encephalopathy
BUN	Blood urea nitrogen
CAR-T	Chimeric antigen receptor T cells
CCS	Container closure system
CD	Cluster of differentiation
CDR	Complementarity-determining regions
CFU	Colony forming unit
cGMP	Current GMP
CHO	Chinese hamster ovary
CI	Confidence interval
CIPC	Critical in-process control
CLL	Chronic lymphocytic leukemia
CMO	Contract manufacturing organization
CofA	Certificate of analysis
CQA	Critical quality attribute
CPK	Creatine phosphokinase
CPP	Critical process parameter
CPV	Continued process verification
CR	Complete response
CRO	Contact research organization
CRS	Cytokine release syndrome
CSR	Clinical study report

CTD	Common Technical Document
CV	Column volume
DCR	Disease control rate
DL	Dose level
DLBCL	Diffuse large B-cell lymphoma
DLT	Dose limiting toxicity
DO	Dissolved oxygen
DOCR	Duration of complete response
DOE	Design of experiments
DOM	Date of manufacture
DOPR	Duration of partial response
DoR	Duration of response
DP	Drug product
DS	Drug substance
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic data capture
E/L	Extractable/leachable
EORTC -QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire
EPC	End of production cells
EQ-5D-3L	EuroQoL 5 Dimensions 3 Levels
EU	Endotoxin unit
FACT-G	Functional Assessment of Cancer Therapy General
FACT-Lym	Functional Assessment of Cancer Therapy–Lymphoma
FAS	Full analysis set
FCP	Final concentrated pool
FDS	Formulated drug substance
FIH	First in human
FL	Follicular lymphoma
FLIPI	Follicular Lymphoma International Prognostic Index
GCB	Germinal center B cell
GCP	Good Clinical Practice
GHS	Global health status
GMP	Good manufacturing practices
HC	Heavy chain
HCP	Host cell protein
HD-ASCT	High-dose chemotherapy followed by autologous blood stem-cell transplantation
HIC	Hydrophobic interaction chromatography

HIV	Human immunodeficiency virus
HLT	High level term
HMW	High molecular weight
HR	Hazard ratio
HRQoL	Health-related Quality of Life
HSA	Human serum albumin
HUV	Hold up volume
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IgE	Immunoglobulin E
IgG4	Immunoglobulin G4
IPC	In-process control
IPI	International Prognostic Index
IPM	In-process monitor
IRB	Institutional Review Board
ICR	Independent central review
ISR	Injection site reactions
IV	Intravenous(ly)
JP	Japanese Pharmacopeia
KIPC	Key in-process control
KM	Kaplan-Meier
KPP	Key process parameter
LC	Light chain
LIVCA	Limit of in vitro cell age
LOD	Limit of detection
LS	Least squares
LTL	Less-than-lifetime
LTT	Long-term treatment
LymS	Lymphoma subscale
MAA	Marketing authorisation application
MBR	Manufacturing batch record
MCB	Master cell bank
MCL	Mantle cell lymphoma
MID	Minimum important difference
MMRM	Mixed model repeated measures
MVM	Minute virus of mice
MZL	Marginal zone lymphoma
NAb	Neutralizing antibody
NCI	National Cancer Institute

NE	Not evaluable
NHL	Non-Hodgkin lymphoma
NK	Natural killer
NOS	Not otherwise specified
ORR	Objective response rate
OS	Overall survival
PAR	Proven acceptance range
PC	Polycarbonate
pCQA	Preliminary CQA
PCR	Polymerase chain reaction
PCSV	Potentially clinically significant value
pcVPC	Prediction-Corrected Visual Predictive Checks
PD	Progressive disease
PDA	Parenteral Drug Association
PFS	Progression free survival
Ph Eur	European Pharmacopeia
PI3K	Phosphoinositide 3 kinase
PK	Pharmacokinetic(s)
PPF	Peristaltic pump filling
PPM	Process performance monitoring
PPQ	Process performance qualification
PPS	Per protocol set
PR	Partial response
PRO	Patient reported outcomes
PS80	Polysorbate 80
PT	Preferred term
PTM	Post-translational modification
TAFD	Time after first dose
QoL	Quality of life
QSP	Quantitative systems pharmacology
QW	Weekly
Q2W	Every 2 weeks
Q4W	Every 4 weeks
R2	Rituximab
RBC	Red blood cell
RP2D	Recommended phase 2 dose
R/R	Relapsing/remitting
RS	Reference standard
SAE	Serious adverse event

SAF	Safety analysis set
SAP	Statistical analysis plan
SC	Subcutaneous(ly)
SCE	Summary of clinical efficacy
SD	Standard deviation
SPC	Statistical process control
SUB	Single use bioreactor
TFF	Tangential flow filtration
TMP	Trans membrane pressure
TOR	Time out of refrigeration
TSE	Transmissible spongiform encephalopathy
TTC	Threshold of toxicological concern
TTDD	Time to definitive deterioration
TTNALT	Time to new anti-lymphoma therapy
TTR	Time to response
UF/DF	Ultrafiltration/diafiltration
USP	United States Pharmacopeia
UV	Ultraviolet
VAS	Visual analogue scale
VCD	Viable cell density
VI	Viral Inactivation
WCB	Working cell bank
WFI	Water for injection

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Regeneron Ireland Designated Activity Company submitted on 26 July 2023 an application for marketing authorisation to the European Medicines Agency (EMA) for Ordspono, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 13 October 2022.

Ordspono, was designated as an orphan medicinal product EU/3/22/2656 and EU/3/22/2649 on 18 July 2022 in the following conditions: diffuse large B-cell lymphoma and follicular lymphoma respectively.

Following the CHMP positive opinion on this marketing authorisation and at the time of the review of the orphan designation by the Committee for Orphan Medicinal Products (COMP), this product was withdrawn from the Community Register of designated orphan medicinal products on 18 July 2024 on request of the sponsor. The relevant orphan designation withdrawal assessment report can be found under the 'Assessment history' tab on the Agency's website: www.ema.europa.eu/en/medicines/human/EPAR/Ordspono

The applicant applied for the following indications:

Ordspono as monotherapy is indicated for the treatment of adult patients with relapsed or refractory follicular lymphoma (r/r FL) after at least two prior systemic therapies.

Ordspono as monotherapy is indicated for the treatment of adult patients with relapsed or refractory diffuse large B cell lymphoma (r/r DLBCL), not otherwise specified (NOS), including DLBCL arising from indolent lymphoma, and high grade B cell lymphoma after at least two prior systemic therapies, including patients with or without prior CAR T therapy.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8(3) of Directive 2001/83/EC - complete and independent application.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

1.3. Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0197/2023 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0197/2023 was not yet completed as some measures were deferred.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

1.5. Applicant's requests for consideration

1.5.1. Conditional marketing authorisation

The applicant requested consideration of its application for a Conditional marketing authorisation in accordance with Article 14-a of Regulation (EC) No 726/2004.

1.5.2. New active substance status

The applicant requested the active substance odronextamab contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.6. Scientific advice

The applicant received the following scientific advice on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
28 October 2020	EMEA/H/SA/4631/2/2020/III	Dieter Deforce and Alexandre Moreau
9 March 2021	EMA/SA/0000049550	Hrefna Gudmundsdottir and Larissa Higgins

The scientific advice pertained to the following non-clinical and clinical aspects:

- The need for additional fertility or reproductive/developmental toxicology studies with odronextamab to support marketing authorisation;
- The designs of the phase 1 study R1979-HM-1333, phase 2 study R1979-ONC-1625, and observational study R1979-ONC-2090 to support, altogether, a marketing authorisation application of odronextamab monotherapy in adults with relapsed or refractory DLBCL after 2 prior lines of systemic therapy;

1.7. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Filip Josephson Co-Rapporteur: Karin Janssen van Doorn

The application was received by the EMA on	26 July 2023

The procedure started on	17 August 2023
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	6 November 2023
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	21 November 2023
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	20 November 2023
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	14 December 2023
The applicant submitted the responses to the CHMP consolidated List of Questions on	26 February 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	02 April 2024
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	11 April 2024
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	25 April 2024
The applicant submitted the responses to the CHMP List of Outstanding Issues on	29 May 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	18 April 2024
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Ordspono on	27 June 2024
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product	27 June 2024

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The indications approved by the CHMP are:

- *Ordspono as monotherapy is indicated for the treatment of adult patients with relapsed or refractory follicular lymphoma (r/r FL) after two or more lines of systemic therapy.*

- *Ordspono as monotherapy is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (r/r DLBCL), after two or more lines of systemic therapy.*

2.1.2. Epidemiology and risk factors

Non-Hodgkin lymphomas (NHLs) comprise the seventh most common malignancy and account for approximately 4.5% of all cancers occurring in the US. In Europe, the estimated incidence of NHL was 122,979 in 2020 with a mortality of 49,684 (Global Cancer Observatory, 2020).

The largest proportion of NHLs (>90%) are of B cell origin, and the remainder are T/natural killer cell lymphomas (Teras, 2016).

2.1.2.1. FL

FL is the most common indolent lymphoma in the US and Europe, accounting for approximately 25% of all B-NHLs. The median age at diagnosis of FL is 65 years.

Autoimmune disease and some occupational exposures have been identified as risk factors of FL.

2.1.2.2. DLBCL

DLBCL is the most common lymphoma, accounting for approximately 30% of all cases of NHL (Chihara, 2022).

The median age at diagnosis of DLBCL is 65 years.

A family history of lymphoma, autoimmune disease, HIV infection, hepatitis C virus seropositivity, a high body mass as a young adult and some occupational exposures have been identified as risk factors of DLBCL (ESMO guidelines 2015).

2.1.3. Biologic features

NHLs comprise a heterogenous group of malignancies that arise from haematopoietic progenitor cells.

B cell NHLs arise from B-lymphocytes and have the cell surface characteristics of normal B-cell differentiation, those with greater lineage maturation express the CD20 marker. Overall, CD20 expression is prevalent but is variable both between and within different lymphoma subtypes (Olejniczak, 2006).

2.1.3.1. FL

FL tumour cells are considered to be malignant counterparts of normal germinal centre B cells in the lymph nodes. Morphologically, the malignant B-cells typically forms a follicular growth pattern.

2.1.3.2. DLBCL

DLBCL tumour cells are thought to arise from B-cells that pass through the maturation steps in the germinal centre, or shortly after, in the lymph nodes. Morphologically, as the name implies, the malignant cells are large and have a diffuse growth pattern without respecting normal tissue/lymph node architecture, often with a high proliferation rate.

2.1.4. Clinical presentation, diagnosis and stage/prognosis

NHLs are commonly grouped into those that exhibit an initially indolent clinical course (such as FL) and those that have a typically aggressive clinical course (such as DLBCL).

2.1.4.1. FL

Patients typically present with asymptomatic lymphadenopathy; however, the majority of patients are diagnosed with advanced disease (Ann Arbor Stage III/IV).

FL has a variable clinical behaviour, ranging from an indolent course over decades to a clinically more aggressive course with increasing refractoriness and decreasing duration of response to therapy. As the disease recurs, patients are treated with multiple lines of therapies during their lifetime.

Transformation to an aggressive lymphoma occurs at a rate of 19% over 8 years and is associated with poor survival outcome (Wagner-Johnston, 2015).

Patients with advanced FL are not cured with available conventional therapies. The 5-year survival rate is approximately 90% and 10-year survival is around 75% (Sarkozy, 2019).

The FLIPI is the most widely used prognostic scoring system to predict survival in newly diagnosed patients, dependent on identified clinical risk factors (age > 60 years, stage III-IV, hemoglobin < 120 g/L, number of nodal areas > 4, and serum LDH level above normal).

A higher risk of death is observed in patients with early progression of disease, specifically within 24 months of commencing first-line immunochemotherapy (Casulo, 2017, Seymour, 2019).

According to the applicant, patients who have received ≥2 prior therapies have a particularly poor prognosis, with a median PFS ranging from 1 to 1.1 years for third-line patients decreasing to 0.5 years for sixth-line patients with a corresponding median OS of 4.8 to 8.8 years and 1.9 years, respectively (Alperovich, 2016, Batlevi, 2020, Rivas-Delgado, 2019).

2.1.4.2. DLBCL

Patients often present with rapidly enlarging lymph nodes or extranodal sites and B symptoms (unexplained fever > 38^{o} C, drenching night sweats, > 10% weight loss over 6 months).

Large B-cell lymphoma (LBCL) is a fast growing, aggressive subtype of NHL with a median survival of less than 1 year if left untreated.

Clinical risk factors have been identified to assess prognosis in aggressive NHLs, using the International Prognostic Index (IPI). Patients with 2 or more risk factors (age > 60 years, performance status 2-4, stage III-IV, extranodal involvement > 1 site, serum LDH > normal) have a less than 50% chance of relapse-free survival and overall survival (OS) at 5 years.

Molecular markers have been identified that are known to confer a poor prognosis, in particular MYC, BCL 2, and BCL-6 rearrangements, as well as molecular prognostic characteristics defined by gene expression profiling (Schmitz, 2018).

With the current standard of care, approximately 60% of patients with DLBCL can be cured (He, 2021).

Patients with r/r DLBCL after 2 or more lines of therapy have a poor prognosis, often with CR-rates between approximately 30-50% reported from different treatment options. A median OS of approximately 6 months in the third- or later lines setting of r/r DLBCL are observed (Radford, 2019).

2.1.5. Management

2.1.5.1. FL

Observation (watch-and-wait) is the standard practice for asymptomatic patients with low tumour burden FL. In the frontline setting guidelines recommend that treatment is only initiated upon occurrence of symptoms, or continuous progression with threatened organ function, or one or more of the modified GELF criteria (including, but not restricted to, bulky disease and cytopenias).

When systemic treatment is indicated, immunochemotherapy with an anti-CD20 monoclonal antibody and chemotherapy, or monotherapy with an anti-CD20 monoclonal antibody, is the first-line standard of care.

Patients who progress after 1 line of therapy may be considered for other standard regimens used in frontline treatment based on their performance status, see Figure below from ESMO Guidelines 2020.

Treatment decisions for r/r FL are influenced by several aspects such as efficacy and duration of prior therapy, tumour burden, presence of symptoms, age and comorbidities.

The combination of (i) lenalidomide with rituximab, and (ii) obinutuzumab with bendamustine are the only available therapies that have full approvals in the EU in second line for patients with r/r FL.

In the third line setting, available treatment options include certain treatment options approved for first- and/or second-line FL. Options for these patients also include CAR-T products (axicabtagene ciloleucel, tisagenlecleucel), CD20xCD3 bispecific antibody (mosunetuzumab), PI3K inhibitors, BTK inhibitor, and radioimmunotherapy.

CAR-T products have been recently approved in r/r FL $\geq$ 2 L (Kymriah) and $\geq$ 3 L (Yescarta). For example, Yescarta has showed efficacy of 91% ORR, 77% CR, and 38.6 months DoR. However, CAR-T products are associated with 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 and accelerated approval in the US 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.

PI3K inhibitors (idelalisib and duvelisib) are approved in r/r FL $\geq$ 2L. According to the applicant, as a class of medications, the PI3K inhibitors used for treating patients with FL yield CR rates between 1% to 8% and the utility of PI3K inhibitors for patients with FL is limited due to safety issues.

In addition, the BTK inhibitor Brukinsa was recently approved in EU, in combination with obinutuzumab, for the treatment of adult patients with r/relapsed FL who have received at least two prior systemic therapies.

Relapsed/ refractory FL is a life-threatening disease with poor prognosis that remains incurable, and therapies that improve PFS and OS are lacking for these patients. Therefore a significant unmet medical need remains in patients with r/r FL who have received ≥2 prior therapies, for additional off-the-shelf treatment options that are effective and have an acceptable safety profile.

Figure 1 Treatment algorithm for high tumour burden FL from ESMO Guidelines 2020

**Of note, CAR-T products and bispecific antibody mosunetuzumab were not approved in the EU in 2020.*

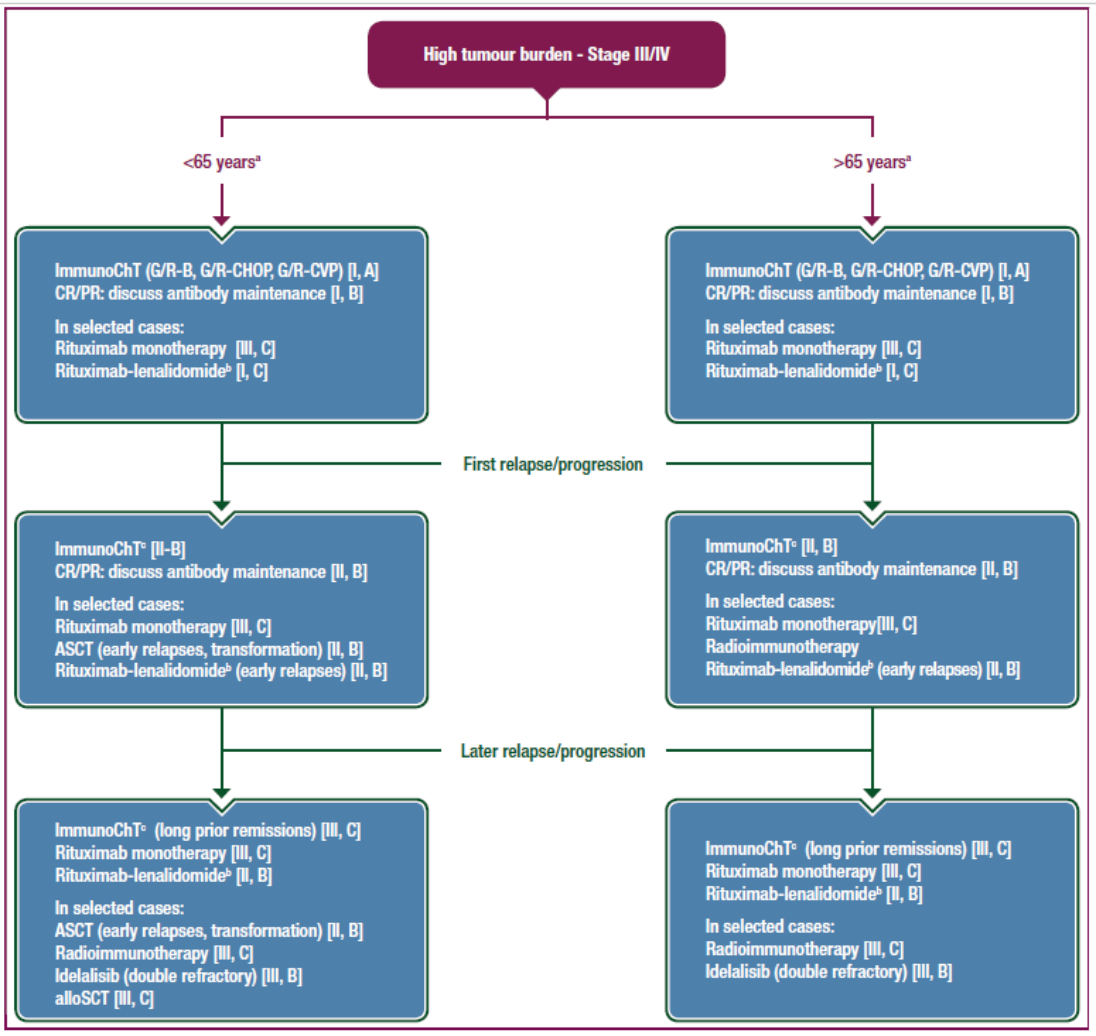


Figure 3. Consensus-driven recommendations—high tumour burden FL

alloSCT, allogeneic stem cell transplantation; ASCT, autologous stem cell transplantation; B, bendamustine; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisolone; ChT, chemotherapy; CR, complete response; CVP, cyclophosphamide, vincristine, prednisolone; FL, follicular lymphoma; G, obinutuzumab; PR, partial response; R, rituximab.

[a] Biological age (years).

[b] Off-label.

[c] Preferred in rituximab-refractory cases.

2.1.5.2. DLBCL

Approximately two-thirds of patients with DLBCL are considered to be cured with first line R-CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone) treatment, but the remaining patients suffer from refractory or relapsed disease (Wang 2020).

Patients with relapsed or refractory disease are often treated with chemoimmunotherapy regimens (including R-ICE [rituximab, ifosfamide, carboplatin, etoposide phosphate] or R-DHAP [rituximab, dexamethasone, cytarabine, cisplatin]) followed by autologous stem cell transplantation (ASCT) if the disease is chemotherapy sensitive and if the patient can tolerate the aggressive treatment. However, patients with chemotherapy-insensitive disease (approximately 35%) and/or are ineligible for ASCT (approximately 50%) have poor prognosis with a median OS of 4 months reported (Friedberg, 2011).

Recently, 2 CAR-T products were approved for use in patients with DLBCL who relapsed within 12 months after or primary refractory to first-line treatment (Yescarta and Breyanzi). The progression-free survival (PFS) for these therapies is approximately 15 months, indicating that there is still an unmet medical need for novel therapies, as stated by the applicant. The use of CAR-T therapy might not be feasible for patients with comorbidities or for patients with progressive disease during CAR-T manufacture that precludes administration of this therapy.

In patients who are ineligible for ASCT or CAR-T, regimens such as gemcitabine and oxaliplatin, or polatuzumab vedotin plus bendamustine and rituximab are treatment options in 2nd line. In addition, the CD19-directed antibody tafasitamab has a conditional approval in the EU since 2021, in combination with lenalidomide for adult patients with relapsed or refractory (R/R) DLBCL who are not eligible for ASCT.

For patients with r/r DLBCL after 2 or more lines of therapy, three anti-CD19 CAR-T therapies (Yescarta, Breyanzi, Kymriah) have marketing approvals in the EU. However, as stated by the applicant, the prognosis for patients who achieve less than a complete response after CAR-T therapy is poor. In addition, as CAR-T products are also approved in 2nd line, there are more limited options for patients in the third line setting.

Loncastuximab tesirine, a CD19-directed antibody and alkylating agent conjugate, was granted a conditional approval in the EU for r/r DLBCL after 2 or more lines of therapy, with ORR of 48%, CR of 25%, and median DoR of 13 months.

Recently, the CD20/CD3 bispecific antibodies glofitamab (ORR 50%, CR 35%, mDoR 14 months) and epcoritamab (ORR 62%, CR 39%, mDoR 16 months) were a granted conditional marketing authorisation in the EU. Confirmatory studies are awaited.

However, even if recent therapies have improved outcome measures for relapsed or refractory DLBCL patients, there remains an unmet medical need for efficacious treatment options in these patients that can potentially overcome mechanisms of resistance to prior lines of therapy and that are widely accessible for patients with lymphoma.

Table 1 Selected part of NCCN guideline 2023 - for r/r DLBCL in third line.

THIRD-LINE AND SUBSEQUENT THERAPY[q]		
T-Cell–Mediated Therapy		Non-T-Cell–Mediated Therapy
• Anti-CD19 CAR T-cell therapy[r] (if not previously given) (in alphabetical order) ‣ Axicabtagene ciloleucel ‣ Lisocabtagene maraleucel ‣ Tisagenlecleucel[s]	• Bispecific T-cell engager therapy (only after at least two lines of systemic therapy; including patients with disease progression after transplant or CAR T-cell therapy) ‣ Epcoritamab-bysp[s,t] ‣ Glofitamab-gxbm[s,u]	• Loncastuximab tesirine-lpyl[m,v] • Selinexor (including patients with disease progression after transplant or CAR T-cell therapy)[w]

Of note, Selinexor is not approved for r/r DLBCL in the EU.

2.2. About the product

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 a polyclonal cytotoxic T-cell response, which results in redirected lysis of the targeted cells, including

malignant B cells. This effect occurs without regard to T-cell receptor specificity or reliance on MHC Class 1 molecules on the surface of antigen-presenting cells.

The initially claimed indications were:

- Ordspono as monotherapy is indicated for the treatment of adult patients with relapsed or refractory follicular lymphoma (r/r FL) after at least two prior systemic therapies.

- Ordspono as monotherapy is indicated for the treatment of adult patients with relapsed or refractory diffuse large B cell lymphoma (r/r DLBCL), not otherwise specified (NOS), including DLBCL arising from indolent lymphoma, and high grade B cell lymphoma after at least two prior systemic therapies, including patients with or without prior CAR T therapy. The proposed posology is described in the following table.

Table 2: Recommended dose

		r/r FL	r/r DLBCL	
Day of treatment		**Dose of Ordspono**		**Duration of infusion**
Cycle 1[a] (Step-up dosing)	Day 1	0.2 mg		Administer Ordspono as a 4-hour infusion.
	Day 2	0.5 mg		
	Day 8	2 mg		
	Day 9	2 mg		
	Day 15	10 mg		
	Day 16	10 mg		
Cycles 2 to 4[a]	Day 1	80 mg	160 mg	Administer Ordspono 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.
	Day 8	80 mg	160 mg	
	Day 15	80 mg	160 mg	
Maintenance (Every 2 weeks)	Begin 1 week after the end of Cycle 4	160 mg	320 mg	Administer Ordspono as a 1-hour infusion every two weeks until disease progression or unacceptable toxicity.
Maintenance (Every 4 weeks)	If a patient is in complete response (CR) for 9 months, administer the Ordspono maintenance dose every 4 weeks.	160 mg	320 mg	Administer Ordspono as a 1-hour infusion every 4 weeks until disease progression or unacceptable toxicity.
r/r FL=relapsed or refractory follicular lymphoma; r/r DLBCL=relapsed or refractory diffuse large B-cell lymphoma [a] For Cycles 1 to 4, a treatment cycle is 21 days.				

Ordspono should be administered until disease progression or unacceptable toxicity.

2.3. Type of Application and aspects on development

The applicant requested consideration of its application for a Conditional Marketing Authorisation in accordance with Article 14-a of Regulation (EC) No 726/2004, based on the following criteria:

- The benefit-risk balance is positive.
- It is likely that the applicant will be able to provide comprehensive data.

The Applicant proposes the provision of the results of two randomized Phase 3 studies, one in R/R FL (R1979-HM-22102 [OLYMPIA 5]) and one in R/R DLBCL (R1979-HM-2299 [OLYMPIA 4]) as Specific Obligations to convert the CMA to a full MAA (details of these trials are discussed under Clinical Efficacy and under the Benefit/Risk section).

- Unmet medical needs will be addressed, as

odronextamab is intended to treat FL and DLBCL which are life-threatening diseases, and is an orphan medicinal product for the treatment of FL and DLBCL. Indirect comparisons indicate that odronextamab efficacy and safety (CRS) results compare favourably to other approved/conditionally approved therapies in this patient population with high unmet need, suggesting a major therapeutic advantage over these therapies. Furthermore, unlike CAR-T, odronextamab is an off-the shelf option, enabling easier access to patients.

- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required.

Given the limited treatment options available and significant unmet medical need in R/R FL grade 1-3a and in R/R DLBCL, these data establish odronextamab as an efficacious treatment option with a favourable risk-benefit and can therefore support the target indication of odronextamab for the treatment of adult patients with R/R FL or R/R DLBCL after at least two prior systemic therapies.

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as concentrate for solution for infusion containing 2 mg, 80 mg and 320 mg, respectively of odronextamab active substance (AS).

Other ingredients are L-histidine, L-histidine monohydrochloride monohydrate, sucrose, polysorbate 80 and water for injection.

The product is available in type I glass vial with a chlorobutyl stopper and a pack size of one vial.

2.4.2. Active substance

2.4.2.1. General Information

The active substance odronextamab is a bispecific anti-CD20xCD3 recombinant human IgG4-based antibody composed of two different heavy chains and a common light chain. One canonical N-glycosylation site is present in each heavy chain (at Asn^{303} in chain 1: HC and Asn^{299} in chain 2: HC*, respectively). The heavy chains have been engineered to minimize Fab arm exchange via hinge substitutions and FcG receptor binding has been reduced via IgG2 substitutions in the respective CH2 domains. Differential Protein A binding of the heavy chains has been engineered via substitution (inactivation) of a HC* Protein A binding site. The amino acid sequence and the properties of the bispecific antibody are acceptably presented in the dossier.

Odronextamab is designed to bridge CD20-expressing cells with cytotoxic T-cells, which results in T-cell activation and CD20-directed polyclonal T-cell killing in an MHC-independent manner.

The information provided in this section is found acceptable.

2.4.2.2. Manufacture, process controls and characterisation

Manufacturers

Odronextamab active substance is manufactured by Regeneron Pharmaceuticals, Inc, 81 Columbia Turnpike, Rensselaer, New York 12144, USA.

Satisfactory demonstration of GMP compliance has been presented.

Description of manufacturing process and process controls

Description of the manufacturing process

The target protein is produced by a fed-batch cell culture process with recombinant Chinese hamster ovary (CHO) cells. The process begins with thawing a frozen vial of the working cell bank (WCB) and expansion through a series of seed train bioreactors. Protein expression occurs in the production bioreactor. The contents of the production bioreactor are harvested by direct depth filtration and polish filtration. Protein product is further purified using a series of packed bed chromatographic and membrane filtration techniques. The resulting filtered final concentrated pool is used to generate active substance (AS), which can be directly formulated with excipient solutions to produce formulated active substance (FAS, direct formulation), or stored frozen until required for formulation (non-direct formulation).

Note, the AS/FAS designations of the Applicant are used in this assessment report. No requirements are made towards the Applicant to change the terminology in the documentation provided.

Descriptions of Process Operations

Descriptions of the process operations are provided, including the assignment of critical process parameters (CPP) and associated in-process controls (IPCs) to each unit operation. Representative chromatograms are provided in the process validation reports), for all chromatography steps. This is assessed to be acceptable.

The manufacturing process is well described, both in flow charts and in detailed narrative descriptions.

Reprocessing

Reprocessing is not part of the standard manufacturing process and would only be executed with an approved protocol in tandem with a deviation event in the quality system. The approach is considered acceptable.

FAS Shipping

FAS is shipped according to the provided shipping details to the receiving site. The shipping process is sufficiently well described.

Resin Lifetime, Sanitization and Storage

The usable lifetime of the chromatographic resins was established. The approach is assessed to be acceptable. The cleaning and storage regimen for the columns is sufficiently well described.

Filter Lifetime, Cleaning and Storage

The maximum number of uses of the TFF membranes is validated and in addition, the cleaning and storage sequence of the TFF membranes is sufficiently well described.

Control of materials

Source, history, and generation of the cell substrate

The α-CD3/α-CD20 bispecific antibody odronextamab is comprised of two human IgG heavy chains and a common human kappa light chain. The cloned heavy chains and light chain plasmids encoding odronextamab were introduced into a CHO host cell line. The history of the cell line and how it was developed, the construction of each plasmid, including the main functional features and a plasmid map, are described in sufficient detail. The information provided is in line with ICH Q5B and ICH Q5D.

Preparation and testing of cell banks

The manufacture, qualification and testing of both the current WCB and future WCBs are described. This is accepted since the stability is considered verified.

For the safety testing of the host cell line, the WCB, MCB, LIVCA it is referred to section A2 and process validation data were satisfactory.

Raw Materials

The manufacturing process does not use raw materials of direct animal origin other than Chinese hamster ovary cells. Safety information for biologically sourced materials was provided, where the overall assessment of materials determined that the risk of contamination by adventitious agents (e.g., viruses, prions) is remote.

A qualitative description of the media components have been provided.

Detailed information has been acceptably provided on the chemical raw materials (media, buffer and solution components), with respect to component usage and quality.

Conclusion

The information on the active substance manufacturing process is considered to be acceptable.

Control of critical steps and intermediates

Acceptable definitions are in general presented for parameters and attributes.

The Non-critical Process Parameters are described in the Manufacturing Process Descriptions.

Limits are established for attributes and for CPPs, with details for each parameter and attribute provided. The limits and their background are sufficiently well described and correspond with the manufacturing process description.

Process validation and/or evaluation

Process Performance Qualification (PPQ)

The process was validated through the successful production of lots.

Impurity Clearance

The impurity clearance performance of the manufacturing process was evaluated during PPQ. Clearance was demonstrated for the impurities evaluated. Details and results are acceptably provided.

Extended Hold Times

A summary of the results, including the validated hold times, is acceptably provided.

A summary of the established validated process durations per unit operation is presented. The approach, description, data presentation, results and harmonization with the process description part are assessed to be correct and acceptable.

LIVCA

The purpose of this validation was to establish the maximum limit of in vitro cell age (LIVCA) for the manufacturing process.

The approach and the results presented is assessed to be acceptable.

Column and Filter Cleaning and Storage

A study was performed to demonstrate that the chromatography column sanitization and storage procedures ensure a microbial-free condition following column use in production and column cleaning of process residue, and to establish product clean hold time and sanitization procedures for the TFF membrane. The approaches are acceptable, and the results are acceptably presented.

Resin Lifetime Concurrent Validation

The concurrent validation study protocols are acceptably presented.

TFF Filter Lifetime

The membrane lifetime has been validated. The approach and results are assessed to be acceptable and is acceptably described.

Shipping Validation

The FAS shipping validation was successfully completed.

Manufacturing process development

Process History

Descriptions of the key changes have been properly included. The process history, material usage and process design differences are well described.

Knowledge Space

Thawing and Expansion of the Working Cell Bank: A summary of the knowledge space surrounding the vial thaw step and seed train unit operations have been acceptably presented and is assessed to be in correlation with the process description.

Production Bioreactor: A summary of the knowledge space surrounding the production bioreactor cell culture step have been acceptably presented and is assessed to be in correlation with the process description.

Purification: A summary of the knowledge space surrounding the purification unit operations have been acceptably presented and is assessed to be in correlation with the process description.

Process Comparability: Data Comparisons

To evaluate the impact of the overall manufacturing changes, product quality was assessed and analytical data that support these statements are provided in the comparability reports.

The data provided demonstrates that comparability has been shown.

Characterization: Elucidation of structure and other characteristics

Several orthogonal techniques were employed to analyse the molecular weight and heterogeneity. Taken together, the dossier contains a comprehensive panel of characterization data using state-of-the-art methods to confirm the primary sequence of the AS and identify relevant mAb-related impurities that were observed.

Post translation modification (PTM) profile was investigated. The expected disulfide bonds were confirmed.

The N-glycan structures are sufficiently characterized and O-linked glycosylation has been acceptably addressed in the characterization of odronextamab.

Higher order structure was investigated. All analyses yielded expected profiles and consistent results and, thus, provided an acceptable assessment of higher order structure.

Consistent purity and weight variant distribution was demonstrated. It is agreed that the quality of the material is consistent with respect to composition and purity.

Consistency in terms of charge variant forms was also thoroughly evaluated and demonstrated.

Presence of product-related variants was probed. No concerns are raised.

Overall, the characterization and discussion on observed charge variant profiles is found acceptable.

A range of assays to assess odronextamab binding to CD20 and CD3 as well as induction of T-cell activation, Fc receptor binding and related assays were described.

A description of the potency assay and results have been provided.

Characterization: Impurities

The process-related impurities were addressed. This is found acceptable, and no concerns are raised.

Extensive characterization of product-related impurities has been demonstrated. Comprehensive data from state-of-the-art analytical procedures demonstrate good control over identity and levels of product-related species.

In summary, sufficient clearance or reduction to acceptable levels of all identified process- and product-related impurities has been acceptably demonstrated.

2.4.2.3. Specification

Specifications

A comprehensive set of relevant tests to cover e.g., appearance, quantity, identity, potency, microbiological and general tests and purity are included in the specification. The tests included in the specification have been selected in accordance with the Ph. Eur. or described in more detail in the case of non-compendial methods. Acceptance criteria for release and end of shelf-life are defined. This is in general found acceptable.

Analytical procedures

A description of compendial and non-compendial analytical procedures used to test the odronextamab active substance at release and over the time of stability monitoring was provided. For all methods, the method principle is described, the critical equipment and critical materials are listed, a brief description of the procedure is provided, and determination and reporting of the results is addressed. Provided descriptions of analytical procedures are comprehensive and in general found acceptable.

Validation of analytical procedures

Validation of non-compendial methods included in the specification was described to support the suitability of the methods with respect to e.g., specificity, linearity, accuracy, repeatability, range, quantitation limit, and robustness.

Batch analyses

Results from batch analyses of AS lots and corresponding FAS lots manufactured with the commercial process are presented in support of a consistent manufacture of active substance. Batch-to-batch consistency has been acceptably demonstrated. All results complied with the proposed specification limits.

Justification of specification

The specification limits for the general characteristics tests are based on results obtained on commercial scale batches manufactured to date and Ph. Eur. requirements. This is found acceptable.

Acceptance criteria are found to be sufficiently justified.

The specification limits for bioburden, bacterial endotoxin, and osmolality are found acceptable.

Reference standards

No international or national reference standard is available for odronextamab since it is a new molecular entity.

The odronextamab commercial reference standard program is based on a two-tiered system with a primary- and working reference standard (RS).

Reference standard stability monitoring has been acceptably described.

Container closure

An acceptable description of the container closure system (CCS) has been provided, including a representative drawing.

The CCS has been demonstrated to be suitable for storage of AS and FAS. This is assessed to be correct.

The information in the section is in general considered to be acceptable and sufficient.

2.4.2.4. Stability

Both AS and FAS stability evaluating studies were performed under the intended storage temperature conditions, temperature and humidity stress, direct light exposure, and after freeze/thaw cycles.

Taken together, the data should inform potential degradation pathways and establish recommended storage conditions.

The proposed shelf-life claim can be considered acceptable.

It is acknowledged that one batch of both AS and FAS will be placed on long-term stability every year that manufacturing of such batches occurs. The lot(s) will be tested according to the analysis plan provided. All testing will be performed with validated methods. This is found acceptable.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and pharmaceutical development

Description of the Finished Product

Three presentations of Ordspono are proposed: 2 mg, 80 mg and 320 mg, concentrate for solution for infusion. The volumes are 1, 4 and 16 ml respectively and the concentrations are 2 mg/mL for the 2 mg presentation and 20 mg/mL for the 80 and 320 mg presentations. The concentrate is to be diluted with 0.9% NaCl and for the lowest treatment of 0.2 mg, addition of albumin is proposed to prevent adsorption if an in-line filter is used. The qualitative and quantitative composition of the FP has been provided as well as the function of the components. All excipients in the composition comply with the Ph. Eur. There is some overfill to provide proper extractable volume but no overage. The vials and stoppers are compliant with appropriate Ph. Eur. monographs for primary containers and closures. The information provided in this section is found acceptable.

Pharmaceutical development

The components of the FP with AS and excipients are described. Functions of the excipients are as buffers, surfactants, stabilizer and tonicifier. The excipients are of pharmacopeial grade and compatible with the AS. There are no novel excipients and there are no materials of human or animal origin. When an IV infusion set with a filter is used for the administration of 0.2 mg dose, human serum albumin (HSA) must be added to the IV admixture to prevent the non-specific adsorption of protein to the IV filter.

Formulation development

The Applicant has described the assessment of buffer systems, pH, surfactants and sucrose concentrations.

It is concluded that the formulation development has been acceptably presented with supporting data.

Manufacturing process development

The FP manufacturing process history from clinical to commercial is presented. Few changes have been performed on the FP side. A rationale is provided where there has been a change through FP development with an assessed potential impact to product quality. It was concluded that that the changes during FP process development did not have an impact on FP quality.

A comparability assessment is provided.

The FP manufacturing process parameters and in process controls for the 2, 80 and 320 mg presentations respectively, and how they are classified are displayed with acceptable justifications. The classifications with operating ranges are found acceptable.

Disposable materials and sterilizing filters are described including sterility assurance and leak integrity testing. Other single-use materials used in the FP process are tabled with supplier biocompatibility and physicochemical test results with pass results for Ph. Eur. 3.1.9 Silicone Elastomer for Closures and Tubing. Extractables and leachables risk assessments and studies including elemental impurities have

been performed on the product contacting materials. The results of the representative FP leachable study show there are no leachables of toxicological concern associated with FP manufacturing process.

Container closure system

The CCS consists of 2, 10 and 20 mL type I glass, Ph. Eur. 3.2.1 compliant vials, stoppered with elastomeric, fluororesin-laminated, latex-free sterile stoppers, compliant with Ph. Eur. 3.2.9. An aluminium seal is crimped around the flask neck with flip-off top. Extraction/leachable studies have been performed including elemental impurities. There were no toxicological concerns.

Microbiological attributes

No preservatives are used, sterility is achieved by bioburden reduction filtration, sterility filtration and aseptic filling, the container closure system prevents microbial contamination. The strategy to control microbial contamination is described with CC integrity testing, release testing, PPQ, equipment qualification, filter validation, shipping validation, aseptic processing and environmental monitoring. The information provided is found sufficient and acceptable.

Compatibility

The finished products are liquid solutions for intravenous (IV) administration. The formulations contain 2 mg/mL or 20 mg/mL protein, 10 mM L-histidine, pH 5.8, 10% (w/v) sucrose, and 0.1% (w/v) polysorbate 80. For IV administration in a clinical setting, the FP will be diluted in an IV bag containing 0.9% NaCl. The IV admixture will be administered through an IV infusion set and catheter using an infusion pump. The planned commercial dose range is 0.2–320 mg.

A bracketing approach has been used for the compatibility studies with IV bags and infusion sets of different materials and dose concentrations.

The data for the studies has been provided and it is agreed that compatibility has been sufficiently demonstrated with the studied materials.

For the lowest dose of 0.2 mg with dilute FP in a 100 mL IV bag and with a filter, HSA must be added to a final concentration of 0.04% to prevent adsorption. For higher doses, 0.5, 1 to 10 or 10 to 320 mg, with or without filter is optional, no HSA is needed to be added. The need for the use of material of human origin in combination with Odronextamab have been justified.

2.4.3.2. Manufacture of the product and process controls

Manufacturers

The information provided on manufacturers is considered acceptable. Satisfactory demonstration of GMP compliance has been presented.

Site information has been provided with addresses and responsibilities. A table is provided on the sites responsible for manufacture, release, testing (release, in-process, stability) and labelling/secondary packaging.

Batch formula

Batch components with function, quality reference, nominal composition and batch size ranges are provided in table format. Amounts in grams for both the 2 mg and the 80 and 320 mg presentations are provided. The information provided is accepted.

Description of manufacturing process and process controls

The FP manufacturing process consists of thawing of FAS (amounts defined in batch formula), preparation of dilution buffer, pooling and mixing of FAS, dilution and mixing for the 2 mg/mL presentation, bioburden reduction, filtration, aseptic filling, stoppering, capping and 100% visual inspection. A flow diagram is shown.

The information provided is acceptable.

Total time out of refrigeration (TOR) from end of thaw to after filling including inspection and bulk packaging is defined and also up to the point where once more refrigerated after the filling. The times out of refrigeration have been challenged during the PPQ.

Control of critical steps and intermediates

The manufacturing process with in-process controls and parameters/quality attributes that are classified are presented. The justification of respective classification and the presented operating parameters are found acceptable.

The fill durations are covered by media fills, validated crimp pressure ranges are found the in process validation section.

Process validation and/or evaluation

PPQ runs were performed for each of the 2 mg, 80 mg and 320 mg presentations, originating from different AS batches which is endorsed. All data is presented and it is concluded that the PPQ batches demonstrate a reproducible process.

Media fill qualifications to confirm the aseptic processing are presented. Validation of the sterilising filter is in-line with EMA/CHMP/CVMP/QWP/850374/2015 and compatibility and microbiological retention capacity is demonstrated. Hold time challenges for sterile filtration process have been made and time out of refrigeration limits determined with acceptance criteria.

Sterilisation methods, gamma irradiation, depyrogenation or autoclavation for product contacting materials are sufficiently described. Both the 2 mg/mL and 20 mg/mL are covered by the validation work.

Shipping procedures of the bulk FP to the pack and label facility with shipping validation, configurations and temperature control is provided.

All excipients are of compendial grade, no excipients of human or animal origin are used, this is accepted. However, it is noted that human albumin solution is recommended to prevent adsorption for the 0.2 mg doses when using a filter. The albumin is not co-packed with the product.

2.4.3.3. Product specification

Specifications

The finished product specifications include control of identity, purity and impurities, potency, sterility and other general tests.

Release and end-of-shelf-life specifications for 2 mg, 80 mg, and 320 mg finished product (FP) presentations are provided.

Analytical procedures

Test methods performed for release, or stability testing of the FP are the same as those used for testing the active substance. The only FP specific method that is not pharmacopeial is the identity method, the method is described and adequately validated.

Batch data

Data from the commercial process is presented. Historical lots are also shown. Source of FAS, FP lot no, description, date of manufacture, lot size in vials used reference standard, disposition status and use are tabled. The batch data is found to be within specification and acceptable reproducibility is demonstrated.

Characterisation of impurities

Process related impurities are listed with impurity, source and applied control strategy. Bioburden, endotoxin, particulate matter, elemental impurities, process leachables and nitrosamines are discussed. An acceptable risk assessment on the presence or formation of nitrosamines was provided. It is found that the control strategies for process related impurities are acceptable. The elemental impurities analysis is compliant with ICH Q3D.

Product-related impurities/variants are degradation products or modified protein inherent in FAS or formed during FP manufacture and storage. An acceptable control strategy is found.

Justification of specifications

The specification limits are stated to be based on product understanding and CQAs, manufacturing history and process capability, clinical experience, safety concerns in accordance with regulations and accumulated stability data.

Reference standards

The reference standard is the same as is described for the active substance.

Container closure system

The in-house depyrogenated vials and supplier autoclaved stoppers comply with appropriate pharmacopeia's. The seal cap is described (no product contact). Extractables/Leachables studies were provided and satisfactory.

2.4.3.4. Stability of the product

The results from primary stability batches of each strength (2 mg, 80 mg and 320 mg) are presented.

Long term storage (5°C ± 3°C), accelerated (25°C) and stressed (45°C) stability studies in line with ICH Q5C as well as photostability studies in line with ICH Q1B have been performed.

A post approval stability protocol and commitment for the continued long term stability studies is provided.

Photostability studies according to ICH Q1B demonstrated that light can promote change in stability, therefore long term storage in the secondary packaging is recommended.

The Applicant has performed in-use stability studies to support storage conditions of 24 hours at 2°C to 8°C or 6 hours at 20-25°C for IV admixtures with or without HSA as earlier mentioned. This is accepted for physico/chemical conditions only.

A shelf life of 3 years at long term storage conditions of 5°C±3°C for the 2 mg, 80 mg and 320 mg presentations can be accepted.

2.4.3.5. Adventitious agents

TSE and non-viral adventitious agents

Animal derived materials are not used in the manufacturing process. Sources of animal-derived materials used in early cell line development and banking have been identified and properly addressed and discussed. Statements on TSE/BSE and virus risk from the suppliers are provided. It is agreed that the risk of TSE/BSE is negligible.

The control of mycoplasma, bacteria and fungi is adequately. The MCB, WCB, unprocessed bulks and EPC cells cultured to LIVCA have also been tested. Pharmacopeial methods have been used.

Testing of cell banks for adventitious and endogenous virus and unprocessed bulk testing

Each unprocessed bulk is routinely tested with an in vitro adventitious virus test, this is considered acceptable. For bioburden, mycoplasma, and PCR, test reports have been provided.

The MCB, WCB and the end of production cells cultured to LIVCA have been tested as according to ICH Q5A (R1). The tests all demonstrate freedom of adventitious and endogenous virus in the cell banks. This is accepted.

Viral clearance and RVLP safety factor

An acceptable rationale for the viruses used in virus validation studies and the selected steps is provided.

Worst-case conditions have been used in the validations and in addition the lowest obtained value in the duplicate runs have been used to calculate overall reductions as a conservative measure. Hold, cytotox and viral interference controls have been used. This is accepted.

The effectiveness of the sanitisation of the chromatographic media has previously been examined. Inactivation kinetics for chromatography cleaning solutions is provided for all viruses and the risk of carry-over between runs is sufficiently mitigated.

The safety assessment for RVLPS, retrovirus safety factor summarizes an estimated residual particle per dose finished product which is acceptable.

2.4.4. Discussion and conclusions on chemical, pharmaceutical and biological aspects

The Ordspono dossier is acceptably structured and of acceptable quality.

The target protein odronextamab is produced in CHO cells in a bioreactor operated in fed-batch mode. The purification process consists of a series of packed bed chromatographic and membrane filtration techniques, virus inactivation and virus filtration. The information on manufacture of the active substance is found acceptable.

Differences between the versions of the manufacturing process used during development are clearly described. Comparability between process versions has been fully demonstrated. Regarding comparability for the Finished Product, comparability has been shown.

Manufacturing, preparation and testing of cell banks, including LIVCA, are acceptably presented.

Characterisation of odronextamab was performed using an extensive panel of appropriate state-of-the art methods.

The development and manufacture of the finished medicinal product has been sufficiently described and justifies the chosen formulation as well as the commercial manufacturing process.

The control of the active substance and finished product has been presented in a satisfactory way.

The stability results for the active substance support the proposed shelf-life when stored at the intended storage condition. Hence, the proposed shelf life is found acceptable.

The proposed shelf life for the finished product is 3 years, when stored at the recommended storage condition at 2°C to 8°C, can be accepted.

Acceptable information has been provided to ensure safety of the product with regards to TSE and virus.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The overall quality of Ordspono is considered acceptable when used in accordance with the conditions defined in the SmPC. The different aspects of the chemical, pharmaceutical and biological documentation comply with existing guidelines.

No further recommendations for future quality development have been made.

In conclusion, based on the review of the quality data provided, it is considered that the marketing authorisation application for Ordspono is approvable from the quality point of view.

2.5. Non-clinical aspects

2.5.1. Introduction

Odronextamab is a IgG4 based bispecific antibody recognising CD20 and CD3 and is indicated as monotherapy for treatment of adult patients with relapsed or refractory follicular lymphoma (r/r FL) and relapsed or refractory diffuse large B cell lymphoma (r/r DLBCL). Upon binding to its respective targets, odronextamab mediates a polyclonal T-cell mediated killing of malignant cells. Pharmacology, pharmacodynamic and toxicology has been evaluated in a wide range of studies. Binding to human and cynomolgus CD20 and CD3 was confirmed in in vitro studies. Cynomolgus monkey was considered the pharmacological relevant species further used in toxicology studies.

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

The applicant has performed in vitro and in vivo studies for the evaluation of the pharmacological properties of odronextamab. In addition, safety pharmacology end points were evaluated in the 4- and 16-week GLP compliant repeat-dose toxicology studies.

In vitro studies

In vitro pharmacology studies were conducted in cell lines and primary B and T-cells derived from both human and cynomolgus monkey for the evaluation of binding and activation properties of odronextamab in a wide range of assays. The relevant cell lines employed in the in vitro pharmacology studies were Raji cells and Jurkat cells. Raji cells are derived from human B-cell lymphoma and have

endogenous expression of CD20, whereas Jurkat cells are derived from human T-cells and endogenously express CD3. Primary B and T-cells of human and cynomolgus origin were isolated from whole blood.

In vitro binding properties

Equilibrium Binding Parameters for the binding of odrenextamab to Cell-Surface CD20 and CD3 was determined by means of flow cytometry. Jurkat and Raji cells were incubated with Alexa488-conjugated odronextamab at concentrations ranging from 200nM to 0.001nM.

An additional binding study showed that odronextamab did not bind to either B-cells or T-cells isolated from mouse and rat.

In vitro functional activity

The selectivity and potency of odronextamab was evaluated using a luciferase reporter assay in Jurkat cells, stably transduced with a Nuclear Factor of Activated T cells (NFAT) response element-luciferase reporter. Jurkat/NFAT-luc reporter cells and Raji cells were incubated in the presence of odronextamab at various concentrations. T-cell activation was only detected in the presence of Raji cells, thus indicating that the presence of CD20 positive target cells is necessary for T-cell activation mediated by odronextamab.

Potency and cytokine release were evaluated in whole blood from both human and cynomolgus monkey upon T-cell activation when incubated at various concentrations of odronextamab. The objectives of this study were to evaluate in both human and monkey 1) induction of proliferation of PBMCs 2) T-cell activation and cytokine release in whole blood and 3) T-cell mediated lysis of CD20-expressing cells. Odronextamab was able to induce proliferation in both human and monkey PBMCs in the presence of a co-stimulatory anti-CD28 antibody at a similar potency level, EC50 55 pM for human and 33.3 pM for monkey PBMCs, albeit with a somewhat lower fold activation in monkey than in human PBMCs when compared to unstimulated cells, which might reflect the differences in EC50 values for human and monkey CD3, respectively.

In human blood samples, the potential of odronextamab to activate T-cells and induce cytokine release was studied in the context of whole blood derived from 10 donors. As a marker for T-cell activation upregulation of CD69 was evaluated. CD69 up-regulation was observed in all donors, as well as cytokine release in the presence of odronextamab. The induction of cytokine release exhibited greater variability among donors than the up-regulation of CD69, an observation that the applicant speculates might be due to genetic elements that regulate cytokine release but does not have an impact on T-cell activation. Overall, based on the in vitro data on cytokine release there is a limited value in translating these results to a clinical setting for assessment of CRS.

Finally, Whole blood from two donors was evaluated for cytokine release in the presence of anti-human Fc antibody mimicking the presence of ADA. In one donor IFNG was increased with increasing anti-IgG whereas no cytokine release increase was observed in the second donor.

Determination of kinetic and equilibrium binding to human Fc gamma receptors were evaluated. Kinetic analysis was used to determine Kd-values for odronextamab binding to Fc gamma receptors. Odronextamab exhibited no detectable binding to human or cynomolgus FcγR1. In addition, binding to human FcγR1 subtypes were either not detected or weaker than a IgG4 control antibody. Kd-values for cynomolgus FcγRs were higher than the IgG4 control antibody.

The antibody-dependent cellular cytotoxicity (ADCC) of odronextamab was evaluated in the presence of human NK cells as effector cells. Rituximab was used as positive control. No ADCC was observed against either Jurkat or Raji cells. In a second approach evaluating CDC, in the presence of Normal

Human Serum (NHS), odronextamab was shown to mediate weak CDC of Raji cells but not against Jurkat cells.

In vivo studies

The applicant has submitted 3 in vivo studies utilising two in vivo mouse models, consisting of humanized (BRG) mice and immunodeficient NSG mice, to evaluate antitumour activities of odronextamab in a repeat-dose setting.

In the first study, new-born BRG mice humanised for Signal-regulatory protein alpha (SIRPA) were irradiated and subsequently engrafted with CD34-positive hematopoietic progenitor cells (HPCs). At day 0 the mice were administered subcutaneously with Raji cells and immediately treated intraperitoneal (IP) with either 0.4 or 0.04 mg/kg odronextamab, or vehicle administered twice weekly for 4 weeks. Odronextamab was able to suppress tumour growth compared to the negative control IgG1 antibody REGN1932 (that has no cross-reactivity towards CD3 or CD20) or vehicle control. It is however noted that REGN1932 has a tumour growth suppression effect that was intermediary between vehicle control and the 0.04 mg/kg dose of odronextamab.

In the second study, at day 0, NSG mice were co-implanted with Raji cells and human PBMCs followed by administration of an intraperitoneal (IP) dose of odronextamab at doses of 0.004, 0.04 or 0.4 mg/kg, administered twice weekly for 4 weeks. 3 control groups were also included: 1) negative control IgG antibody REGN1932 at 0.4 mg/kg, 2) 0.4 mg/kg odronextamab without engraftment of PBMCs and 3) vehicle control. Odronextamab exhibited a complete suppression of tumour growth compared to the three control groups. Similarly, as in the study performed in BRG mice an intermediary response on tumour growth was noted with the negative control antibody REGN1932. It is unclear why this tumour suppressing effect was observed, and no explanation is provided by the applicant.

In the third study in NSG mice co-engrafted with Raji cells and human PBMCs, effect on cytokine release stimulated by odronextamab was studied. This was done by pre-treatment of mice with rituximab, RTX, which has only affinity to CD20 or an IgG control antibody 13 days after co-implantation with Raji cells and PBMCs. Three doses of RTX were used: 1, 10 and 50 mg/kg. At day 14 mice were administered IP with either odronextamab (0.4 mg/kg) or a CD3 binding control antibody (0.4 mg/kg). In terms of suppression of tumour growth, combination of RTX pre-treatment and odronextamab or odronextamab alone exhibited the most potent effect, both treatment modalities were more or less equally potent. Serum levels of IFNG, IL2, TNFA, IL4, IL8, and IL10 were increased in animals receiving only odronextamab compared to control antibody after 4 hours. Combination of 50mg/kg RTX and odronextamab exhibited the most potent effect of reduced cytokine levels compared to odronextamab alone. Even though this study suggests pre-treatment with RTX as a potential strategy to mitigate odronextamab-associated CRS it is unclear to which extent the presented data is translatable to a clinical setting, and the relevance of the study is questionable.

Overall, the antitumour activity of odronextamab was satisfactorily demonstrated in the conducted in vivo studies. It can be noted that the first two studies are to be considered models of prevention since treatment with odronextamab was administered at the same time as tumour cells. The third study has more relevance in terms of the proof-of-concept since odronextamab was administered 14 days post tumour cell injection.

Finally, Pharmacokinetic characteristics and anti-tumour activity of odronextamab was evaluated in NGS mice implanted SC with both Raji cells and PMBCs (study REGN1979-PH-17078). Higher doses of 0.4 and 0.1 mg/kg resulted in complete tumour suppression whereas lower doses exhibited only reduction in tumour volume. For PK discussion of this study see section 3.2.3 Pharmacokinetics.

B-cell depletion

B-cell depletion is considered a pharmacodynamic marker of odronextamab consistent with its intended mechanism of action. B-cell depletion was evaluated in the dedicated single dose pharmacokinetic study (REGN1979-PK-13085) that aimed to elucidate the PK/PD relationship of odronextamab after a single IV infusion at doses of 0.001, 0.01 and 0.1 mg/kg. The degree of the observed B-cell depletion was dose proportional. An almost complete depletion of B-cells was observed at all doses at early timepoints, i.e., by 24 hours. Repletion of B-cells was also dose proportional with lower serum levels of odronextamab leading to a more complete repletion.

2.5.2.2. Secondary pharmacodynamic studies

No dedicated secondary studies were performed by the applicant. This is considered acceptable.

2.5.2.3. Safety pharmacology programme

Safety pharmacology endpoints were integrated within in the 4- and 16-week GLP compliant repeat-dose toxicology studies at doses up to 1 mg/kg.

Safety pharmacology endpoints of vital organ systems included evaluation of the respiratory function, neurological examinations, and cardiovascular function. Heart rate, pulse oximetry, and respiration rate were collected from anesthetized animals. Neurological examinations were also conducted.

No changes on safety pharmacology endpoints were detected.

2.5.2.4. Pharmacodynamic drug interactions

No dedicated secondary studies were performed by the applicant. This is considered acceptable.

2.5.3. Pharmacokinetics

Pharmacokinetic and toxicokinetic parameters were evaluated in a wide range of single-dose and repeat-studies. The pharmacological relevant species was cynomolgus monkeys that exhibit similar binding properties to human CD3 and CD20. Odronextamab was not able to bind to rat or mouse CD3 or CD20. The use of cynomolgus monkeys in PK/TK studies as a single species is supported. In all non-clinical studies concentrations of total odronextamab, i.e., all drug without regard to binding site occupancy, was measured by means of ELISA. No gender specific differences were detected.

Methods of analysis

In the submitted pharmacokinetic written summary assays are presented. The first one is an ELISA assay used to measure odronextamab in monkey serum. The second one is a flow cytometry-based method used to identify lymphocyte populations and the third is an immunoassay used for the detection of ADA.

The flow cytometry assay is briefly described in the various study reports where identification of lymphocyte populations is being performed.

Absorption

Single dose PK of odronextamab

PK/PD relationship was assessed in a single dose, non-GLP, study (REGN1979-PK-13085) comprising three dose levels, 0.001, 0.01, or 0.1 mg/kg in male cynomolgus monkeys. Within a dose range between 0.001 and 0.01 mg/kg the pharmacokinetics of total odranextamab was non-linear in terms of

concentration time profile and exhibited a brief distribution phase. This was followed by a prolonged beta elimination phase and a target mediated phase. Immunophenotyping analysis of blood samples was performed for the two dose levels 0.001 and 0.01 mg/kg of odronextamab for the evaluation of B-cell depletion and repletion. Briefly, in both dose groups a steep decline of B-cells was noted at 24h post-dose and remained almost completely depleted until 336h post-dose. Persistence of B-cells depletion and subsequent repopulation exhibited a similar pattern in both dose groups. Repopulation of B-cells was noted for both dose groups starting at 672 h post-dose with the exception of one animal in the low dose group of 0.001 mg/kg, that exhibited repopulation of B-cells at 336h post-dose. Predose levels of B-cells for all animals was reached at 1008h post-dose. Overall, B-cell repletion inversely correlated with exposure of odronextamab.

C_{max} increased in a dose proportional manner at all doses and the distribution volume remained at a constant level in all dose levels. In addition, within all dose groups the range of $t_{1/2}$ was 7.9-9.7 days.

Pharmacokinetic characteristics and anti-tumour activity of odronextamab was evaluated in a study using humanised NGS mice implanted SC with a both Raji cells and PMBCs (study REGN1979-PH-17078). The aim of this single dose PK/PD study was to assess the pharmacodynamic characteristics of odronextamab after single IP doses of 0.04, 0.1, 0.4 and 1.0 mg/kg. At higher doses of 0.4 and 0.1 mg/kg resulted in complete tumour suppression while lower doses of 0.04 and 0.1 mg/kg exhibited only reduction in tumour volume. Higher doses of odronextamab (0.4 and 1 mg/kg) exhibited linear PK whereas lower doses (0.04 and 0.1 mg/kg) exhibited non-linear PK. Calculated average concentrations at day 7 (C_{av}/day7) for the higher doses were 2.6 and 6.9 µg/mL and for the lower doses 0.11 and 0.47 µg/mL.

Immunogenicity

In studies where PK/TK were evaluated the presence and potential impact of ADA on pharmacokinetic parameters was evaluated either by using a titre based bridging immunoassay or indirectly through assessment by visual inspection of individual concentration-time profiles. The titre based bridging immunoassay was used in 2 studies.

The impact of ADA was in general considered to be low. In the dedicated single dose PK evaluation study the presence of ADA was not evaluated with any assay validated assay. Nevertheless, based on visual inspection of concentration-time profiles in this study a total of three out of 36 animals exhibited profiles that the applicant considers to be consistent with ADA impact.

In the single dose, GLP-compliant, toxicity study ADA analysis was performed and showed that 3 out of 26 animals had positive ADA responses, albeit weak. No impact on pharmacokinetics of odronextamab was noted. It is worth noting that that of these three animals, one belonging animal belonging to control group had a positive response predose Day 1. The additional two animals belonged to group 5 and 6, i.e, the two dose escalating groups administered either IV or SC with odronextamab.

In the two repeat dose toxicity studies, the presence of ADA was only assayed in the 16-week study. In the 4-week study it was assessed by visual inspection of TK profiles.

In conclusion the presence of ADA can be regarded as having low impact on concentration of odronextamab both in regard to the low number of animals that had detectable levels of ADA, and also with respect to concentration levels of odronextamab.

Overall, odronextamab exhibits an expected pharmacokinetic profile for this class of antibodies.

2.5.4. Toxicology

2.5.4.1. Single dose toxicity

The safety profile of odronextamab was evaluated in female cynomolgus monkeys in a GLP study following a single dose of 0.1 or 1 mg/kg SC or 1 mg/kg IV (Phase I) or escalating doses of 1/25/100 mg/kg (IV and SC; Phase II) with an 8-week recovery period.

Exposure to odronextamab was tolerated in monkeys following IV or SC administration, with both administration routes resulting in rapid and sustained B-cell depletion. Drug-related findings were generally consistent with its intended pharmacology or secondary effects related to T-cell activation, B-cell depletion, cytokine release, and/or presumed opportunistic infections.

2.5.4.2. Repeat dose toxicity

The safety profile of odronextamab was evaluated in cynomolgus monkeys in 2 GLP-compliant repeat-dose toxicology studies following once weekly IV infusions of 0.01, 0.1, and 1 mg/kg for 4 weeks (total of 5 doses) with a 12-week recovery period and following once weekly IV infusions of 0.1 and 1 mg/kg for 16 weeks (total of 17 doses) with a 14-week recovery period.

Toxicokinetic evaluations conducted as part of each in vivo toxicology study demonstrated that continuous exposure to total odronextamab was observed in the majority of animals that received ≥0.1 mg/kg across studies, which supports the relevance of the safety findings discussed herein. Across studies, odronextamab induced B-cell depletion in peripheral blood (evaluated via flow cytometry) by 24 hours postdose for all dose levels, which generally persisted throughout the dosing period in animals administered ≥0.1 mg/kg.

In the repeat-dose toxicology studies, once weekly IV infusion of up to 1 mg/kg odronextamab for up to 4 weeks was tolerated. Findings were generally attributed to T-cell activation, B-cell depletion, cytokine release, and/or presumed opportunistic infections. There were no drug-related effects on vital signs (body temperature, blood pressure, and respiration and heart rate); or respiratory, neurological, or cardiovascular changes evident, nor infusion site reactions. In addition, there were no drug-related effects on fertility endpoints assessed during the 16-week study.

Across studies, odronextamab-related effects consisted of clinical signs related to cytokine release and/or presumed opportunistic infections. These effects included vomitus, hunched posture, emesis, hypoactivity, recumbency, fecal abnormalities, and/or low food consumption. A transient decrease in peripheral T cells followed by slight T-cell activation and an increase in plasma cytokines were seen after the first dose only. These changes were not seen after subsequent doses, consistent with the absence of target cells (B cells). Additional changes associated with odronextamab administration included: decreased white blood cell (WBC) and/or lymphocyte counts, findings consistent with inflammation (increased C-reactive protein [CRP]; decreased albumin, globulins, and/or albumin:globulin ratio; and decreased red cell mass); microscopic observations of decreased B cells in lymphoid organs with secondary effects consistent with B-cell depletion; microscopic findings of mixed cell inflammation and/or an increase in the incidence and/or severity of mixed and/or mononuclear cell infiltrates in several tissues, with mixed cell inflammation of the gastrointestinal organs, liver, gallbladder and/or pancreas correlating with hematologic and/or clinical chemistry indicators of inflammation and hepatobiliary effects.

During the 4- and 16-week repeat-dose studies, several animals were humanely euthanized early due to deteriorating body conditions. All animals had pharmacological B-cell depletion in both peripheral blood and lymphoid organs at the time of unscheduled sacrifice. Clinical signs (fecal abnormalities

often with cultures positive for *Campylobacter* or *Staphylococcus aureus*), increased CRP and neutrophils, and multiorgan inflammation, including of the gastrointestinal tract, were consistent with acute inflammation and attributed to presumed opportunistic infections due to sustained B-cell depletion.

As evaluated in the 16-week study, no anti-keyhole limpet hemocyanin (KLH) IgM or IgG responses were detected in animals administered ≥0.1 mg/kg odronextamab, consistent with its intended pharmacology of B-cell depletion.

2.5.4.3. Genotoxicity

According to the *ICH guideline S2 (R1) on genotoxicity testing and data interpretation for pharmaceuticals intended for human use (*EMA/CHMP/ICH/126642), 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. Therefore, no genotoxicity studies were conducted with odronextamab.

2.5.4.4. Carcinogenicity

As odronextamab is intended for use in patients with advanced malignancies, carcinogenicity studies were not conducted with odronextamab, consistent with *ICH guideline S9 on non-clinical evaluation for anticancer pharmaceuticals* EMA/CHMP/ICH/646107.

2.5.4.5. Reproductive and developmental toxicity

Fertility endpoints were evaluated during the 16-week repeat-dose toxicology study conducted in monkeys (R1979-TX-17190). Male (testicular measurements and semen analysis) and female (menstrual cyclicity) fertility endpoints were evaluated, and microscopic evaluation of male and female reproductive organs was conducted. 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.

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. Administration of odronextamab to cynomolgus monkeys was associated with an increased incidence of infections leading to deteriorating body conditions and the early humane euthanasia of several animals in the general toxicology studies. A similar outcome would be expected if an embryo-fetal developmental toxicology study were conducted, which may interfere with the interpretation of study results. Therefore, a review of the risks associated with targeting both CD20 and CD3 based on published literature and available nonclinical data was completed in lieu of conducting an embryo-fetal developmental toxicology study with odronextamab. Based on its mechanism of action, odronextamab may cause fetal B-cell lymphocytopenia and transient CRS that may be harmful to pregnancy maintenance.

2.5.4.6. Other toxicity studies

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 (3 donors per tissue, where available) and selected fetal human tissues (1-3 donors per tissue, where available).

In both studies, REGN1979-Bio stained the positive controls (CD20-expressing Raji cells and/or CD20-transfected HEK293 cells) and CD3-expressing Jurkat cells, as well as the ancillary controls (human tonsil or fetal human spleen), at both concentrations but did not specifically react with the negative control material at either staining concentration. No staining was observed with the control article. The demonstrated specific reactivity of REGN1979-Bio with the positive control material and the lack of specific reactivity with the negative control material, as well as the lack of reactivity of the control article, indicated that the assays were sensitive, specific, and reproducible.

As expected, based on the known expression of CD20 by B cells and CD3 by T cells, REGN1979-Bio stained the membrane and/or cytoplasm of mononuclear leukocytes in both lymphoid and non-lymphoid tissues in both human (adult and fetal) and monkey tissues. No unanticipated cross-reactivity of the test article was observed in either study.

2.5.5. Ecotoxicity/environmental risk assessment

Odronextamab is a monoclonal antibody and as such it is exempted from an ERA; as a protein it is significantly metabolized in vivo and is expected to be readily and rapidly degraded in wastewater treatment systems and in the environment. Therefore it would not be expected to pose a risk to the environment.

2.5.6. Discussion on non-clinical aspects

Primary pharmacology

Overall, the primary pharmacodynamic studies provided adequate evidence of the pharmacological properties of odronextamab. The applicant has performed a wide range of in vitro and in vivo studies that thoroughly characterise the pharmacological properties of odronextamab. In addition, safety pharmacology was satisfactory evaluated in the 4- and 16-week GLP compliant repeat-dose toxicology studies.

The in vitro pharmacology studies addressed in vitro binding properties and in vitro activation properties of odronextamab in a wide range of assays employing primary B and T-cells from both human and cynomolgus monkey as well as cell lines such as Raji cells that are derived from human B-cell lymphoma and have endogenous expression of CD20, and Jurkat cells that are derived from human T-cells and endogenously express CD3.

In vitro binding and functional activity was established for CD3 and CD20 in cells of human and cynomolgus origin but no binding to the murine variants of the receptors was observed. The corresponding EC_{50} for Jurkat and Raji cells were 11.7 nM and 82.8 nM respectively, reflecting a somewhat weaker binding to CD20 than CD3. The corresponding figure for cells isolated from whole blood for human B-cells was 57.9nM and the corresponding figure for cynomolgus was 61.2nM. For human T-cells it was 37.7nM and 2.35µM for cynomolgus. Whereas the binding of CD20 was within the same concentration range for both human and monkey, there was approximately a 100-fold difference with respect to human and monkey CD3. This observed difference indicates a higher affinity for human CD3 which might be the cause of the observed discrepancy between cytokine levels observed in human and in cynomolgus, respectively.

In vitro functionality assays showed that T cells are activated only in the presence of CD20 expressing cells. In addition, it was shown that odronextamab induce cytokine release in human whole blood.

The antitumour activity was evaluated in 2 mouse models consisting of humanized (BRG) mice and immunodeficient NSG mice engrafted with Raji cells and human CD34-positive HPCs and PBMCs.

Odronextamab was shown to effectively suppress tumour growth at higher concentrations. Interestingly, and unexpectedly the negative control antibody REGN1932 exhibited an intermediary response on tumour growth at levels between that of odronextamab and vehicle control. It was also shown that odronextamab was able to induce cytokine release.

Pharmacokinetics

Single dose pharmacokinetics evaluated in a dedicated PK study showed that within a dose range between 0.001 and 0.01 mg/kg the pharmacokinetics of total odronextamab was non-linear and exhibited a brief distribution phase. This was followed by a prolonged beta elimination phase and a target mediated phase. Within these ranges there was also an observed steep decline in B-cell numbers observed 24h post dose. An evaluation of B-cell depletion was not done at the dose level of 0.1 mg/kg without the applicant any clarifying discussion as to why this was not performed. With increasing doses of 0.01 and 0.1 mg/kg there was a correlation between B-cell depletion and clearance of odronextamab. B-cell repletion inversely correlated with exposure of odronextamab.

C_{max} increased in a dose proportional manner at all doses and the distribution volume remained at a constant level in all dose levels. In addition, within all dose groups the range of $t_{1/2}$ was 7.9-9.7 days.

Finally, dose and concentration dependent depletion of B-cells was observed for the 0.001 and 0.01 mg/kg dose groups. B-cell depletion was not evaluated at the 0.1 mg/kg dose level.

Overall, the pharmacokinetic profile of odronextamab exhibits an expected pattern for this class of products.

Toxicology

In the single- and repeat-dose toxicology studies, odronextamab results in rapid and sustained B-cell depletion, consistent with its intended pharmacology. Across studies, drug-related findings were generally consistent with its intended pharmacology and included T-cell activation and cytokine release, secondary effects related to B-cell depletion, and/or presumed opportunistic infections. These aspects are well understood from clinical safety data, and the animal toxicity studies do not provide additional information for the benefit-risk assessment or for inclusion in the SmPC.

Embryo-fetal developmental toxicology studies were not conducted with odronextamab. A risk assessment based on available nonclinical data and literature was provided. This approach is agreed and is in line with previous CHMP conclusions on other members of this class of bispecific antibodies. Based on literature it is agreed that B-cell elimination in itself is unlikely to represent a risk for embryofetal development. However, in the later phase of pregnancy, transfer of antibodies to the fetus may result in B-cell lymphocytopenia in the newborn baby. Also, the cytokine release and the inflammatory reaction may constitute a risk for the maintenance of the pregnancy. These risks are adequately reflected in Sections 4.6 and 5.3 of the SmPC.

A restrictive recommendation for use during lactation is proposed. Although IgG antibodies are transferred to milk only in a limited amount, it is agreed that for this bispecific antibody with potent immunostimulatory activity such restrictive wording is appropriate (see section 4.6 of the SmPC).

In tissue cross-reactivity studies with cryosection from human and cynomolgus tissues all observed staining was expected based on the known expression of CD20 by B-cells and CD3 by T-cells.

The active substance is a protein- based substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, odronextamab is not expected to pose a risk to the environment.

2.5.7. Conclusion on the non-clinical aspects

The conducted in vitro and in vivo pharmacological studies are considered adequate and the proof of concept of odronextamab is considered demonstrated. Odronextamab was shown to only cross-react with human and cynomolgus CD20 and CD3. The PK and TK are considered well covered. The toxicology program is sufficient.

Relevant information has been included in the SmPC sections 4.6 and 5.3.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

Table 3 Overview of pivotal study 1625 FL

Study / Report Location/ Study Status	Study Population /Analysis Sets	Efficacy-Related Objectives	Study Design, Efficacy Evaluable Patients (with total), and Duration	Treatment: Dose, Route of Administration, Frequency
Phase 2 Studies				
R1979-ONC-1625 Module 5.3.5.2 Ongoing	Men or women ≥18 years of age with B-NHL who relapsed or were refractory to prior systemic therapy	Primary efficacy objective: • To assess antitumor activity of odronextamab in each cohort as measured by ORR (assessed by IRC) Secondary efficacy objectives: • To assess antitumor activity of odronextamab in each cohort as measured by ORR (assessed by local investigator), CR rate, PFS, OS, DOR, and DCR (all assessed by IRC and local investigator) • To evaluate safety and tolerability of odronextamab • To assess PK of odronextamab • To assess immunogenicity of odronextamab • To assess PRO including health-related quality of life	Open-label, multicohort, multicenter study. Efficacy Evaluable Patients: 128 Duration: 12 weeks QW (including step-up dosing) then Q2W dosing until disease progression or other protocol-defined reason for treatment discontinuation. Opportunity to switch from Q2W to Q4W after 9 months	FL grade 1-3a Odronextamab IV, 80 mg[a] QW/160 mg Q2W with step-up dosing.

Study / Report Location/ Study Status	Study Population /Analysis Sets	Efficacy-Related Objectives	Study Design, Efficacy Evaluable Patients (with total), and Duration	Treatment: Dose, Route of Administration, Frequency
			of maintained CR	

B-NHL = B-cell non-Hodgkin lymphoma;; FL = follicular lymphoma; IRC = independent central review; IV = intravenous; PK = pharmacokinetics; QW = once every week; Q2W = once every 2 weeks; Q4W = every 4 weeks.

a. The first full QW dose (Cycle 2 Day 1) was administered as single IV infusion if no cytokine release syndrome grade ≥3 was observed in cycle 1, otherwise it was administered as a split infusion over 2 days. Starting with Cycle 2 Day 8, QW doses were administered as a single IV infusion.

To support the proposed indication in **r/r DLBCL**, the applicant has submitted data from the pivotal phase 2 study 1625 and the supportive phase 1 study 1333, which included a DLBCL cohort in patients with DLBCL who had progressed after CAR-T therapy.

Table 4 Overview of pivotal study 1625 DLBCL

Study / Report Location/ Study Status	Study Population /Analysis Sets	Efficacy-related Endpoints	Study Design, Efficacy Evaluable Patients (with total), and Duration	Treatment: Dose, Route of Administration, Frequency
Phase 2 Studies				
R1979-ONC-1625 Module 5.3.5.2 Ongoing	Men or women ≥18 years of age with B-NHL who relapsed or were refractory to prior systemic therapy.	Primary efficacy endpoint: • To assess antitumor activity of odronextamab in each cohort as measured by ORR (assessed by IRC) Secondary efficacy endpoints:	Open label, multicohort, multicenter study. Efficacy Evaluable Patients: 127 Duration: 12 weeks QW (including step-up dosing) then Q2W dosing until disease progression or other protocol-defined reason for treatment discontinuation. Opportunity to switch from Q2W to Q4W after 9 months of maintained CR	DLBCL cohort • Arm 1: Odronextamab IV, 160 mg[a] QW/320 mg Q2W with step-up dosing. • Arm 2: Odronextamab IV, 320 mg[b] QW/320 mg Q2W with step-up dosing.

Study / Report Location/ Study Status	Study Population /Analysis Sets	Efficacy-related Endpoints	Study Design, Efficacy Evaluable Patients (with total), and Duration	Treatment: Dose, Route of Administration, Frequency
		• To assess antitumor activity of odronextamab in each cohort as measured by ORR (assessed by local investigator), CR rate, PFS, OS, DOR, and DCR (all assessed by IRC and local investigator) • To evaluate safety and tolerability of odronextamab • To assess PK of odronextamab • To assess immunogenicity of odronextamab • To assess PRO including health-related quality of life		

B-NHL = B-cell non-Hodgkin lymphoma; CD = cluster of differentiation; DLBCL = diffuse large B-cell lymphoma; IRC = independent central review; IV = intravenous; PK = pharmacokinetics; QW = once every week; Q2W = once every 2 weeks; Q4W= once every 4 weeks

a. The first full QW dose (Cycle 2 Day 1) was administered as single IV infusion if no cytokine release syndrome grade ≥3 was observed in cycle 1, otherwise it was administered as a split infusion over 2 days. Starting with Cycle 2 Day 8, QW doses were administered as a single IV infusion.
b. The first full 320 mg QW dose (Cycle 2 Day 1) in Study 1625 was administered as a split 160/160 mg IV infusion over 2 days and as a single infusion (320 mg) after Cycle 2 Day 1 if tolerated.

Table 5 Overview of supportive study 1333 which included a DLBCL-after-CAR-T-cohort.

Study / Report Location/ Study Status	Study Population /Analysis Sets	Efficacy-related Endpoints	Study Design, Efficacy Evaluable Patients (with total), and Duration	Treatment: Dose, Route of Administration, Frequency
Phase 1 Studies				
R1979-HM-1333 Module 5.3.5.2 Ongoing	Men or women >18 years of age with documented CD20+ B-cell malignancy, with active disease not responsive to prior therapy, for whom no	Primary efficacy endpoint:	Open-label, multi-center, dose escalation study Efficacy Evaluable Patients: 44	DLBCL after CAR-T Odronextamab IV, 160 mg[a] QW/320 mg Q2W with step-up dosing.

Study / Report Location/ Study Status	Study Population /Analysis Sets	Efficacy-related Endpoints	Study Design, Efficacy Evaluable Patients (with total), and Duration	Treatment: Dose, Route of Administration, Frequency
	standard of care options exist, and for whom treatment with an anti-CD20 antibody could be appropriate. Patients with BNHL must have previously been treated with CD20-directed antibody therapy	• To assess safety, tolerability, and DLTs • To evaluate odronextamab concentrations in the aggressive lymphoma (excluding patients with prior CAR-T therapy) and FL grade 1-3a, expansion cohorts that may correlate with toxicity, and potential antitumor activity • To study antitumor activity in DLBCL after failure of CAR-T therapy expansion cohort as assessed by IRC <u>Secondary efficacy endpoint:</u> • To characterize the PK profile • To assess immunogenicity • To assess antitumor activity of odronextamab in each cohort as measured by ORR (assessed by local investigator). CR rate, PFS, OS, DOR, and DCR (all assessed by IRC and local investigator) • To study the antitumor activity in aggressive lymphoma (excluding patients with prior CAR-T therapy) and FL grade 1-3a as assessed by local investigator evaluation and IRC	Duration: 12 weeks QW (including step-up dosing) then Q2W dosing until disease progression or other protocol-defined reason for treatment discontinuation.	

B-NHL = B-cell non-Hodgkin lymphoma; CAR-T = chimeric antigen receptor T cells; CD = cluster of differentiation; CSR = clinical study report; DLBCL = diffuse large B-cell lymphoma; DLT = dose-limiting toxicity; FL = follicular lymphoma; IRC = independent central review; IV = intravenous; PK = pharmacokinetics; QW = once every week; Q2W = once every 2 weeks;

a. The first full QW dose (Cycle 2 Day 1) was administered as single IV infusion if no cytokine release syndrome grade ≥3 was observed in cycle 1, otherwise it was administered as a split infusion over 2 days. Starting with Cycle 2 Day 8, QW doses were administered as a single IV infusion.

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

Descriptive pharmacokinetic data for odronextamab are provided from the two clinical studies supporting the efficacy and safety assessment (Studies 1333 and 1625). Specific studies on elimination, distribution or pharmacokinetic interactions have not been performed and are not considered necessary for an antibody. Pharmacokinetics in special populations have been evaluated by population pharmacokinetic (PK) analyses. The step-up regimen was derived from a Quantitative Systems Pharmacology (QSP)-model that was developed with the objective to describe the dynamic profiles of IL-6 in response to odronextamab IV, and ultimately suggest an odronextamab step-up dosing regimen for clinical evaluation. The PK and pharmacokinetic-pharmacodynamic (PK/PD) analyses were performed to describe odronextamab concentrations in serum in adult patients with R/R B-NHL and variability and to characterize the relationship between exposure-efficacy/safety.

Bioanalytical methods and ADA detection

Bioanalytical methods were developed and validated to assess concentrations of total odronextamab, as well as immunogenicity to odronextamab (with anti-drug antibody [ADA] and neutralising antibody [NAb] assessments) in human serum.

Quantification of odronextamab serum levels

An ELISA was developed and validated to determine the concentrations of total odronextamab in human serum. The assay employs a microtiter plate coated with a mouse anti-odronextamab monoclonal antibody (mAb), specific for the anti-CD20 binding site of odronextamab, and uses odronextamab as a standard. Odronextamab captured on the microplate is detected using a different biotinylated mouse anti-odronextamab mAb, specific for the anti-CD3 binding site of odronextamab, followed by NeutrAvidin conjugated with horseradish peroxidase (NeutrAvidin-HRP). A luminol-based substrate specific for peroxidase is then added to achieve a signal intensity that is proportional to the concentration of total odronextamab.

Anti-drug antibody (ADA) methods

Two ADA assays were developed and validated to monitor immunogenicity in the odronextamab clinical program.

The initial ADA method was used to evaluate samples in dose escalation levels 1 through 14 (odronextamab 0.030 mg - 40 mg) in Study 1333. A second assay was subsequently validated with an improved drug tolerance limit (DTL) that exceeded steady state trough odronextamab concentrations at the proposed, to-be-marketed dose. The second ADA assay was used to analyse samples from patients in Study 1333 in dose levels 15 and above (including expansion; odronextamab 80 mg - 320 mg;), and for patients in Study 1625 at all dose levels.

Both ADA assays were non-quantitative, titer-based assays that potentially involves three tiers in evaluation of a sample: an initial screening assay to identify samples that are potentially positive for anti-drug antibodies (ADA); a confirmation assay to determine if a positive response in the screening can be inhibited by the presence of excess unlabelled drug and a titer assay to assess levels of ADA in positive samples. The electrochemiluminescence (ECL) assay procedure uses a mouse anti-odronextamab mAb specific for the CD20 binding site of odronextamab as a positive control

(REGN2985). As CD3 positive control, the first assay (BMP-PCL4244) employed a polyclonal rabbit-anti-odronextamab antibody (REGN3862). The second assay (BMP-PCL5409) utilised a monoclonal mouse anti-odronextamab antibody as CD3 positive control (REGN2805). Biotinylated odronextamab and ruthenium-labelled odronextamab were used as bridge components. The assays employ a floating cut point to determine positive responses.

Neutralising antibody (NAb) assay

In this assay, odronextamab activates CD3+ T cells (effector cells) in the presence of CD20-expression cells (target cells). The bioassay uses Jurkat cells (effector cells) that have been stably transfected with an NFAT-Luciferase (Jurkat/NFAT-Luc) reporter gene containing a puromycin resistance marker and HEK-293 cells transfected to express CD20 (HEK-293/CD20).

Jurkat/NFAT-Luc cell activation in the presence of odronextamab and HEK-293/CD20 cells is measured as luminescence and is reported as relative light units (RLUs). The amount of NFAT-Luc RLUs is directly proportional to the concentration of odronextamab added to the assay. Anti-odronextamab NAb will block binding of odronextamab, thus inhibiting the induced NFAT-Luc activation and result in lower RLU responses.

Evaluation and Qualification of the Population PK Model

The PK of odronextamab was evaluated in Study 1625 and Study 1333. Concentration-time profiles by dose cohorts were described and summary statistics of exposure parameters are presented for both studies. The objectives of this analysis were to develop and assess the performance of a population PK model to describe odronextamab concentrations in serum in adult patients with R/R B-NHL, to characterize sources and correlates of variability in odronextamab concentrations, including the influence of intrinsic and extrinsic factors, and to generate post hoc metrics of odronextamab exposure.

Development of a base structural model that described the concentration-time profile of odronextamab in serum leveraged prior knowledge on (a) typically reported PK behaviour of monoclonal antibodies, (b) odronextamab mechanism of action, and (c) preliminary odronextamab PK. The covariate model building process consisted of two separate covariate testing approaches combined: the full covariate modelling approach (absolute correlation coefficient, R, of > 0.7, only the most significant covariate was considered), and the step wise covariate model approach (with forward inclusion and backward deletion).

The final analysis set contained concentration data from 507 patients (14618 concentration records) with B-NHL (FL, DLBCL, MCL, MZL, other B-NHL), including 166 patients with FL and 261 patients with DLBCL, who received odronextamab at doses ranging from 0.03 mg to 320 mg in both studies. Post-dose concentration records that were BLQ represented 3.4% (n=515) and were excluded from the analysis. Most patients were diagnosed as having either R/R DLBCL or R/R FL (52% and 33%, respectively). The remaining of the patients had either R/R MCL, R/R MZL, or other type of R/R B-NHL lymphoma with a prevalence of less than 10% each. Most of the patients were White (62%), male (62%), with median age of 65 [inter-quartile range, IQR: 55 - 72] years, body weight of 72.6 [IQR: 61.35 - 84] kg, with an ECOG score of 1 (60%), Ann Arbor stage of 4 (62%), and albumin in serum of 38.7 [IQR: 34 - 42] g/L.

Odronextamab concentration-time profiles following IV administration of 0.03 mg to 320 mg doses was described by a bi-exponential decline with parallel linear (first-order) and non-linear (Michaelis-Menten) elimination processes. The Michaelis-Menten or target-mediated elimination typically only concentration-dependent – was modified to also include a time-dependent component.

Table 6. Parameter Estimates of the Base, Full, and Fit-For-Purpose Models

Parameter	Estimate (95% CI) (run523; base model)	Estimate (95% CI) (run533; full model)	Estimate (95% CI) (run573; fit-for-purpose model)
Linear clearance, CL (L/day)	0.176 (0.169 — 0.184)	0.191 (0.187 — 0.196)	0.189 (0.185 — 0.194)
- Albumin effect on CL		-0.967 (-1.13 — -0.8)	-0.933 (-1.1 — -0.769)
- Body weight effect on CL		0.807 (0.739 — 0.876)	0.854 (0.783 — 0.925)
- Immunoglobulin G effect on CL		0.136 (0.109 — 0.162)	0.118 (0.0912 — 0.145)
- Interferon gamma effect on CL			0.0274 (0.0173 — 0.0375)
- Interleukin 10 effect on CL			-0.0717 (-0.0833 — -0.0601)
Intercompartmental clearance, Q (L/day)	1.31 (1.22 — 1.41)	1.19 (1.11 — 1.28)	1.21 (1.13 — 1.29)
Volume of distribution of central compartment, V_c (L)	4.73 (4.56 — 4.91)	4.63 (4.48 — 4.78)	4.99 (4.8 — 5.2)
Volume of distribution of peripheral compartment, V_p (L)	4.11 (3.73 — 4.53)	4.1 (3.73 — 4.5)	4.42 (4.01 — 4.87)
- Albumin effect on V_c and V_p		-0.551 (-0.739 — -0.364)	-0.561 (-0.742 — -0.379)
- Body weight effect on V_c and V_p		0.561 (0.444 — 0.679)	0.372 (0.242 — 0.501)
- Female sex effect on V_c and V_p			-0.186 (-0.24 — -0.133)
- Lymphocyte count effect on V_c and V_p		0.0887 (0.0556 — 0.122)	0.0895 (0.0576 — 0.121)
Baseline maximum velocity of Michaelis-Menten elimination, V_{max0} (mg/L/day)	2.1 (1.91 — 2.3)	2.4 (2.04 — 2.82)	2.93 (2.56 — 3.36)
- Ann Arbor stage <4 effect on V_{max0}			-0.285 (-0.375 — -0.195)
- Lymphocyte count effect on V_{max0}		0.32 (0.247 — 0.392)	0.313 (0.242 — 0.384)
- Follicular lymphoma effect on V_{max0}		-0.229 (-0.369 — -0.0877)	-0.252 (-0.367 — -0.137)
- Other B-NHL type effect on V_{max0}		0.0776 (-0.164 — 0.319)	

Figure 2. All B-NHL subpopulations, population prediction-corrected Visual Predictive Check

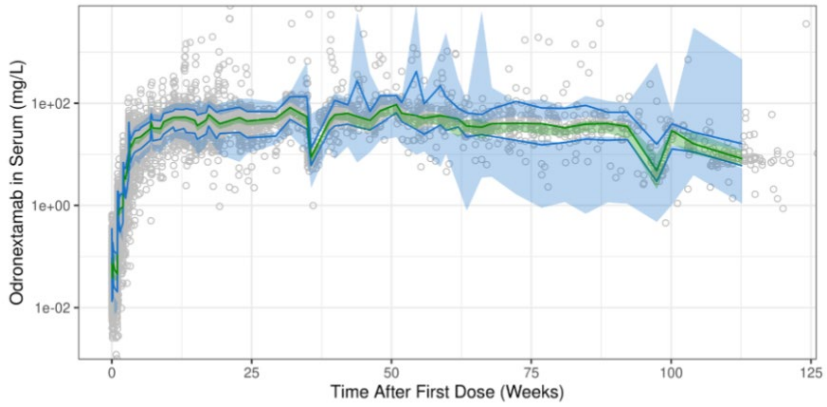
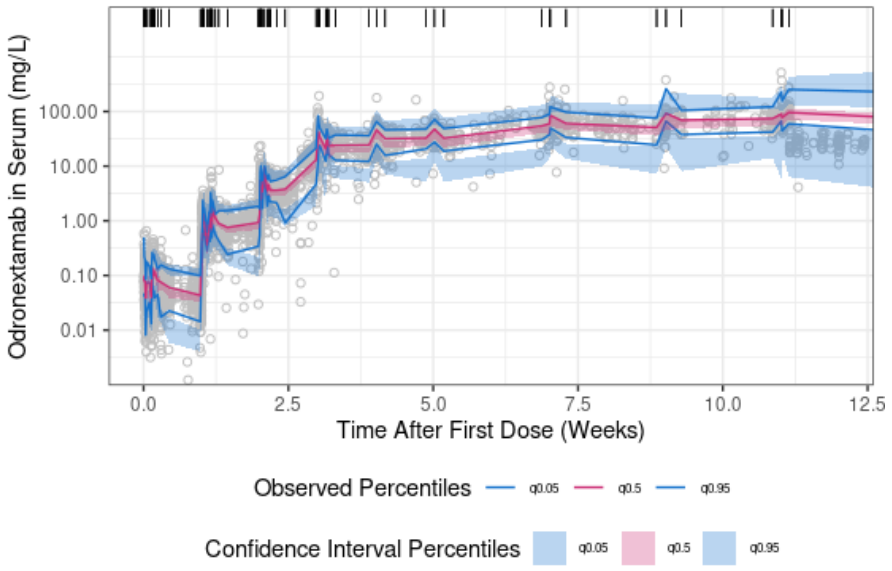
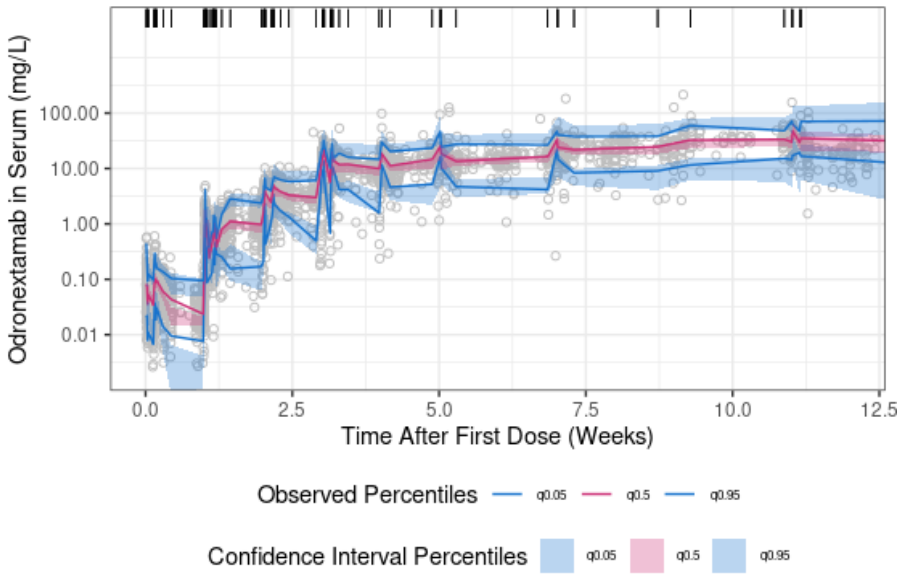


Figure 3 Concentration vs TAFD for Week 0-12 (pcVPC) in DLBCL patients.



As observed percentiles generally covered by the model-based confidence intervals, this indicates that the model adequately predicts the observed data by indication and by bodyweight quartiles.

Figure 4 Concentration vs TAFD for Week 0-12 (pcVPC) in FL patients.



Most 95% CI of covariate effects on odronextamab exposure relative to reference were contained within the 80-125% range, except for body weight, albumin, and IL-10. The estimated effects of these important covariates on Cmin,ss relative to the reference patient were:

- A 49.8-kg (5 th percentile) or 111-kg (95 th percentile) patient was estimated to have 1.47-fold (95% CI: 1.42, 1.51) and 0.632-fold (95% CI: 0.609, 0.657) change, respectively.
- A patient with albumin level of 28.3 g/L (5th percentile) or 46 g/L (95 th percentile) was estimated to have 0.689-fold (95% CI: 0.65, 0.733) and 1.22-fold (95% CI: 1.18, 1.25) change, respectively.

- A patient with an IL-10 level of 0.6 ng/L (5th percentile) or 79 ng/L (95 th percentile) was estimated to have 0.871-fold (95% CI: 0.852, 0.892) and 1.3-fold (95% CI: 1.25, 1.36) change, respectively.

Absorption

There are no dedicated clinical biopharmaceutic studies, as odronextamab is administered intravenously.

A comparison of odronextamab drug products manufactured using two different processes in patients with FL grade 1-3a (80 mg QW) and DLBCL (160 mg QW) was performed using descriptive analyses of observed odronextamab C_{trough} at week 12. There is no apparent effect of drug products on odronextamab exposure with similar C_{trough} values for both manufacturing processes. This observation is consistent with *in vitro* data, where analytical comparability was demonstrated. With regard to the drug product and drug substance, reference is made to the quality assessment.

Distribution

Odronextamab is expected to primarily distribute in the vascular system. The population estimated steady-state volume of distribution was 9.34 (48.5%) L (geometric mean [CV% of geometric mean]).

Elimination

The metabolism of odronextamab is expected to be limited to proteolytic catabolism into small peptides and individual amino acids by the endoplasmic reticulum system.

The population PK analysis indicated that over the totality of the doses studied (0.03 mg to 320 mg) and observed concentrations, the concentration-time profile of odronextamab exhibited a bi-exponential decline with parallel linear (first-order) and non-linear (Michaelis-Menten) elimination processes, which is typical of a protein therapeutic exhibiting target-mediated elimination. The estimated clearance at steady-state for the 160 mg Q2W dose and for the 320 mg Q2W dose were approximately 5% to 6% of baseline clearance in week 1 (4.32 L/day) in patients with B-NHL.

At steady-state, the predicted time required for odronextamab concentrations to decline to 1% of the median C_{max} of the last 160 mg Q2W dose was 12 weeks, and the predicted time required to decline to 1% of the median C_{max} of the last 320 mg Q2W dose was 16 weeks.

Due to the concentration- and time-dependent clearance, a fixed half-life value cannot be adequately determined.

Dose proportionality and time dependencies

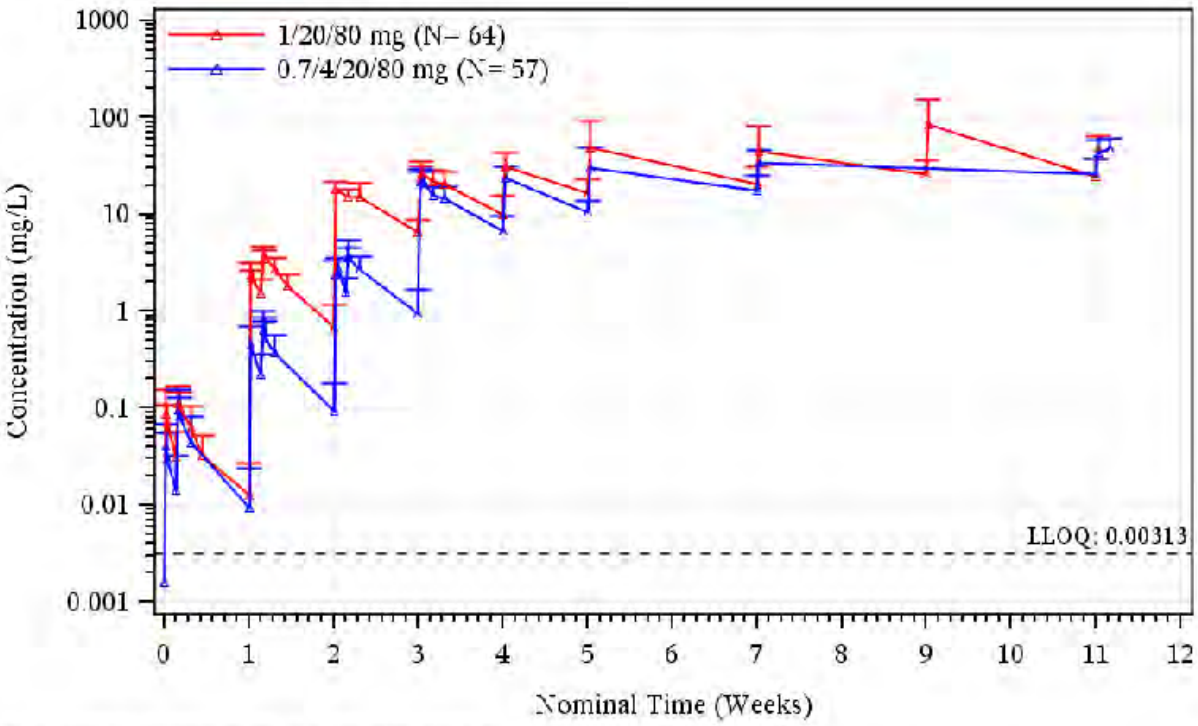
At initiation of treatment with step-up doses, odronextamab exhibited rapid, nonlinear target-mediated clearance. The rate of decline in serum concentrations was faster at the initial step-up doses administered in early weeks (weeks 1 to 3) than at higher doses (80 mg to 320 mg) at week ≥4. With continued dosing at higher dose levels (80 mg to 320 mg), the PK of odronextamab approached a linear and dose proportional profile. Some degree of time-dependency was likely present during the first weeks as target-mediated clearance decreased when B-cell count decreased.

Pharmacokinetics in target population

Two step-up regimens were studied in Study 1625 (ie, the 1/20 regimen and the 0.7/4/20 regimen). As expected, based on the slower step-up during cycle 1, the observed odronextamab exposures with the 0.7/4/20 regimen were lower in weeks 1 to 3 than with the 1/20 regimen (**Error! Reference source not found.** and **Error! Reference source not found.**). By week 4, following administration of the first maintenance dose (80 mg or 160 mg) plasma concentrations were largely similar regardless of step-up regimen used.

Following the first maintenance doses in week 4, steady state was reached by week 12. In FL (80 mg dose), C_{max} and C_{trough} increased 2.5-fold and 4.6-fold, respectively, from week 4 to week 12. In DLBLCL (160 mg dose) C_{max} and C_{trough} increased 2.8-fold and 5-fold, respectively, from week 4 to week 12.

Figure 5. Mean (+SD) Concentrations of Total Odronextamab in Serum from Participants with FL in First 12 Weeks by Nominal Time and Dose Regimen (Study R1979-ONC-1625, Log-Scaled)

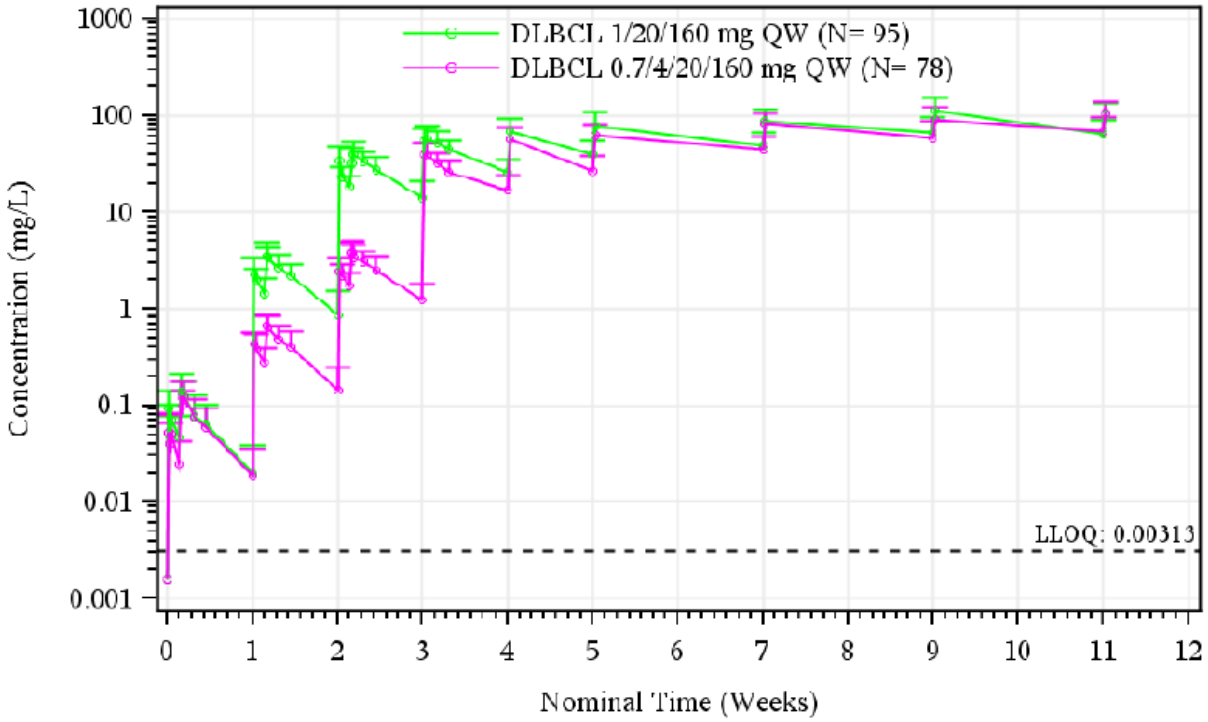


N = Number of participants in each dose regimen

Note: Below LLOQ value is set to LLOQ/2. Initial and the intermediate step-up doses >=1 mg were split equally and administered over 2 consecutive days. The initial dose of 0.7 mg was split as 0.2 mg/0.5 mg over 2 consecutive days. For each timepoint, only participant who received planned doses per protocol with concentration results are included, also n>=2.

/sasdata/Data/Production/PK/R1979/R1979-ONC/R1979-ONC-1625/Interim/Interim_202303/Analysis_CSR/Programs/TFL/Figures/f_pcmmlogflupw12.sas (qiao.qin :09JUN23:14:08 SAS Linux 9.4)

Figure 6. Mean (+SD) Concentrations of Total Odronextamab in Serum from Participants with DLBCL in First 12 Weeks by Nominal Time and Dose Regimen (Study R1979-ONC-1625, Log-Scaled)



DLBCL, Diffuse large B-cell lymphoma; LLOQ, Lower limit of quantification; N, Number of patients in each dose regimen; PKAS, Pharmacokinetic analysis set; QW, Weekly; SD, Standard deviation
Note: Below LLOQ value was set to LLOQ/2. Initial and intermediate step-up doses ≥1 mg were split equally and administered over 2 consecutive days. The initial dose of 0.7 mg was split as 0.2 mg/0.5 mg over 2 consecutive days. For each time point, only patients who received planned doses per protocol with concentration results were included, n ≥2.
Treatment weeks 1 to 3 correspond to cycle 1, weeks 4 to 6 to cycle 2, weeks 7 to 9 to cycle 3, and weeks 10 to 12 to cycle 4.

When comparing concentration-time profiles under the 0.7/4/20 regimen in patients with FL or DLBCL, respectively, odronextamab C_{trough} were lower in the first week in FL than in DLBCL. The lower C_{trough} of odronextamab in week 1 in patients with FL is consistent with a higher B-cell baseline count observed in patients with FL, presumably leading to greater target-mediated clearance in patients with FL during week 1.

Starting at week 4 of the first 80 mg QW dose or 160 mg QW dose, the concentration-time profiles increased dose proportionally and this was consistent across different disease-specific cohorts at a given regimen, regardless of B-NHL subtype. These data indicate that beyond the first 1 to 2 weeks with low doses of odronextamab, tumour type had no continuing impact on PK of odronextamab.

The population PK analysis indicated that with a 160 mg Q2W regimen, C_{trough} of odronextamab is similar to those achieved with 80 mg QW, supporting the selection of 160 mg Q2W for maintenance in FL patients. Likewise, with a 320 mg Q2W regimen, the C_{trough} of odronextamab was similar to that achieved with the 160 mg QW regimen.

With a switch to the Q4W regimens, i.e. halving of the dose by increasing the dose interval, in subjects who had a CR of 9 months, C_{trough} concentrations decreased, as expected. Maintained disease control with this regimen is discussed under Clinical Efficacy below.

Immunogenicity

In the overall population (ie, all patients from Study 1625 and Study 1333), the incidence of treatment-emergent ADA was 1.5% (6/400) as determined through 30 months of evaluation. These treatment-emergent ADA were indeterminate (0.8% [3/400]) or transient (0.8% [3/400]) responses; all were low titer (<1000). NAb positive responses were not observed. There was no evidence that the odronextamab exposure was affected by the treatment-emergent ADA status. The 6 patients with treatment-emergent ADA had similar odronextamab exposure compared with patients who had no treatment-emergent ADA.

Special populations

No clinically relevant differences in exposure to odronextamab were observed based on age (22 to 89 years; N=507), sex, race [white (N=316), Asian (N=129), or Black (N=7)], body weight, renal impairment, or mild to moderate hepatic impairment. Specific studies in renally or hepatically impaired patients were not conducted. The influence of renal impairment (based on calculated CLcr) and hepatic impairment (based on total bilirubin and AST) on odronextamab PK was assessed by population PK analysis.

Renal function was not identified as a significant covariate of drug exposure in the population PK analysis. However, increasing steady-state odronextamab exposure was observed to increase with increasing severity of renal impairment. Notably, a consistent trend of lower body weight with increasing renal impairment was observed. As body weight is a known covariate of exposure for mAbs in general as well as for odronextamab, the observed increase in exposure with decreased renal function is most likely explained by the effect of body weight.

No clinically relevant differences in exposure to odronextamab were observed in patients with normal hepatic function and with mild (N=78; total bilirubin > ULN to 1.5 x ULN or AST > ULN) and moderate (N=5; total bilirubin > 1.5 to 3 x ULN and any AST) hepatic impairment. The effects of severe (total bilirubin > 3 to 10 x ULN and any AST) hepatic impairment on the PK of odronextamab are unknown.

Sex was found to be a significant covariate in the population PK model, however, the impact on exposure was small and is not considered clinically relevant.

Body weight had the largest effect on odronextamab exposure. Patients with body weight within the 0-0.05 quartile range [31.8, 49.8 kg] (N=26) or within the 0.95-1 quartile range [111, 165 kg] (N = 27) had a median steady-state C_{min} that was 1.68-fold and 0.629-fold, respectively, relative to the reference patient.

No apparent PK differences were observed due to race (white (N=316), Asian (N=129), or Black (N=7)) or age.

Table 7 ***Participants by Age Group in Studies 1625 and 1333 (PKAS)***

	Age 65-74 (Older subjects number /total number)	Age 75-84 (Older subjects number /total number)	Age 85+ (Older subjects number /total number)
R1979-HM-1333	67/167	26/167	4/167
R1979-ONC-1625	104/340	54/340	3/340
Combined	171/507	80/507	7/507

Pharmacokinetic interaction studies

No pharmacokinetic interaction studies were performed. As it is known that transient elevations of cytokines may suppress CYP450 enzymes, a warning has been included in section 4.5 of the proposed SmPC that odronextamab might affect substrates of CYP450s during the first weeks of treatment.

2.6.2.2. Pharmacodynamics

Mechanism of action

Odronextamab is a bispecific CD3-CD20 T-cell engager, designed to bind CD20-expressing target cells and cross link them to CD3-expressing T cells, resulting in T-cell activation and generation of a polyclonal cytotoxic T-cell response.

Primary and Secondary pharmacology

Odronextamab pharmacodynamics (PD) was assessed in Study 1625 and Study 1333 and characterized by (i) depletion of B cells, (ii) redistribution and expansion of T cell, and (iii) transient cytokine elevation.

Engagement of cytotoxic T-cells and tumour cells expressing CD20 results in immune mediated lysis of tumour cells.

For a monoclonal antibody, no secondary pharmacological effects are expected.

Pharmacodynamics and Pharmacokinetics-Pharmacodynamics (PK/PD)

The efficacy variables objective response (OR), Complete response (CR), overall survival (OS) and progression free survival (PFS) were used in the exposure-efficacy analysis, assessed in relation to the exposure metrics C_{trough} week 12 and AUC 0-12 weeks. In both patients with FL and DLBCL, C_{trough} at week 12 and AUC0-12 week was observed to significantly increase the overall and complete response rate. The response rate was similar between C_{trough} at week 12 and AUC0-12 weeks. Based on the exposure-response analyses of efficacy, the median exposure for the proposed dosing for FL and DLBCL, respectively, is predicted to result in around 89% and 56% of ORR, and 78% and 41% of CRR were predicted for FL and DLBCL patients at median exposure respectively.

The safety variables used in the exposure-safety analysis were Grade 0 versus grade ≥ 1 infections, Grade < 3 versus grade ≥ 3 infections, and cytokine release syndrome (CRS, grade 0 versus grade ≥ 1), relationship assessed with exposure metric AUC 1, 2, 3, and 4 weeks. Safety analysis indicated that CRS events were not directly associated with exposure after week 2. For infection, FL patients tend to have grade ≥3 infection at later time point compared to DLBCL patients in the combined analysis.

2.6.3. Discussion on clinical pharmacology

The PK of odronextamab administered as an IV-infusion to subjects with DLBCL and FL is adequately described. No specific studies were performed to evaluate distribution, protein binding, elimination mechanisms or pharmacokinetic drug interactions for odronextamab, which is acceptable for an antibody.

No studies in patients with renal or hepatic impairment were performed. This is acceptable as odronextamab is expected to be eliminated via target-mediated clearance and normal, proteolytic

catabolism, and therefore not affected by renal or hepatic function. In patients with mild hepatic impairment (N=78) and patients with moderate hepatic impairment (N=5), no notable differences in the exposure of odronextamab were found in comparison with patients with normal hepatic function. No dose adjustment is recommended for patients with mild to moderate hepatic impairment. Ordspono has not been studied in patients with severe hepatic impairment (total bilirubin > 3 to 10 x ULN and any AST). This information has been reflected in section 4.2 of the SmPC. No dose recommendations can be made for patients with severe hepatic impairment (see SmPC section 4.2 and 5.2). Accordingly, renal or hepatic impairment were not identified as significant covariates of odronextamab exposure in the population pharmacokinetic analysis.

Overall, the methods for detection of odronextamab in serum and for anti-odronextamab antibodies (ADAs) are considered to have been validated in accordance with the EMA Guideline on bioanalytical method validation (EMEA/CHMP/EWP/192217/2009 Rev. 1).

The population PK model is mainly descriptive (i.e. has relatively low regulatory impact) and mostly considered as supportive evidence. The overall model building approach appears reasonable, except for the covariate selection process. The covariate selection included two steps (full model approach and stepwise selection) which is a limitation which may have led to inclusion of a more-than-optimal number of covariate-parameter relationships in the final PopPK model. Based on the model diagnostics, it appears adequate for use of deriving post-hoc exposures for exposure-response analysis for the DLBCL and FL populations. However, the model should not be used for simulations or extrapolation, prior to covariate model re-examination. pcVPCs were provided for the pooled B-NHL subpopulations as well as the DLBCL and FL populations, respectively. According to the pcVPCs, the model gave acceptable description of the observed data. Of note, the 5th percentile of the observed data was slightly under-predicted for the DLBCL subpopulation according to Figure 3 (indicating that the model slightly over-predicts the variability in DLBCL patients). Since the model gave acceptable description of the median profile and no other meaningful model misspecifications were evident, this issue is not pursued further. Additional pcVPCs based on time since the most recent dose, and stratified by body weight groups indicated acceptable description of the observed data (data not shown).

The effects of intrinsic and extrinsic factors on the PK of odronextamab were evaluated through population PK analysis. The population PK analysis indicated that bodyweight was the co-factor with highest impact on exposure, which is expected for an antibody distributed mainly to the vascular compartment. Patients with body weight within the 0-0.05 quartile range [31.8, 49.8 kg] (N=26) or within the 0.95-1 quartile range [111, 165 kg] (N = 27) had a median steady-state C_{min} that was 1.68-fold and 0.629-fold, respectively, relative to the reference patient. Although the same odronextamab dose is recommended regardless of weight according to the SmPC, this difference in exposure across weight is of considerable magnitude with unknown impact on efficacy or safety.

For renal impaired patients, it is agreed that the increase in odronextamab exposure observed with decreased renal function was likely rather due to the fact that mean bodyweight decreased with decreasing renal function.

Since the risk for a clinically relevant interaction cannot be excluded, at least not for P450 substrates with a narrow therapeutic index, the SmPC Section 4.5 includes a warning that the transient increase in cytokine levels during the first weeks of treatment might suppress P450 enzymes and thereby affects concomitantly administered CYP450 substrates. A recommendation to monitor such substrates has been added.

The PK/PD models are mainly descriptive (relatively low regulatory impact) and mostly considered as supportive evidence. The primary objectives of the PK/PD analysis were to characterise exposure-efficacy and exposure-safety relationships in adult patients with R/R DLBCL or R/R FL enrolled in studies R1979-HM-1333 and R1979 ONC-1625. The exposure metrics used in the analysis were C_{trough}

at week 12 (for efficacy), AUC 0-12 weeks (for efficacy), and AUC 1, 2, 3, 4 weeks (for safety), derived using the population PK model. The efficacy variables that were used in the exposure-efficacy analysis were objective response (OR), Complete response (CR), overall survival (OS) and progression free survival (PFS). The safety variables used in the exposure-safety analysis were Grade 0 versus grade ≥ 1 infections, Grade < 3 versus grade ≥ 3 infections, and cytokine release syndrome (CRS, grade 0 versus grade ≥ 1).

In patients with FL as well as DLBCL, $AUC_{0\text{-}12\ week}$ was observed to significantly increase the overall and complete response rate. The response rate was similar between C_{trough} at week 12 and $AUC_{0\text{-}12\ week}$. Although these trends in response versus exposure are rather inconclusive they raise the question if subjects with higher body weight possibly could have a lower response rate.

Safety exposure-response analyses indicated that CRS events were not directly associated with AUC on weeks 1-4 after week 2. For infection, FL patients tend to have Grade ≥3 infection at later time point compared to DLBCL patients in the combined analysis.

The applicant developed a QSP model to characterise the IL-6 release during odronextamab step-up administration of evenly split doses, with the objective to derive a step-up regimen to be evaluated in the pivotal 1625 study. The data used for model development was limited and the diagnostic plots were insufficient to draw a secondary conclusion on how well the model performs. The Applicant recognises the limitations of the model, however, given the objective of the model this is acceptable considering that the weight and the impact of this model are also relatively limited.

2.6.4. Conclusions on clinical pharmacology

The PK of odronextamab administered as an IV-infusion to subjects with DLBCL and FL is sufficiently well characterised and is adequately described in relevant sections of the SmPC.

2.6.5. Clinical efficacy

2.6.5.1. Dose response studies

Rationale for selection of step-up doses for FL and DLBCL

During the dose escalation part of Study 1333, the safety of multiple step-up dosing regimen was tested empirically from 0.03/0.1 mg to 1/20 mg in the first 2 weeks. Based on this empiric approach, the step-up regimen was originally set as 1 mg in week 1 (administered as split doses of 0.5 mg on day 1 and 0.5 mg on day 2 of cycle 1), and 20 mg in week 2 (administered as split doses of 10 mg on day 8 and 10 mg on day 9 of cycle 1) (ie, the 1/20 regimen). This 1/20 regimen was implemented in the dose expansion part of Study 1333 and in Study 1625.

From the accumulated data obtained with the 1/20 regimen from both studies combined, a rate of 9% grade ≥3 CRS was observed in all treated patients with B-NHL. At this point in development, there was a pause in enrollment in both studies, due to a partial clinical hold imposed by the FDA, during which the sponsor revised the step-up dosing regimen to mitigate the risk of CRS.

Optimization of the step-up dosing regimen was performed by using a QSP model, which characterized dynamic profiles of IL-6, a representative cytokine associated with CRS. The developed QSP model was utilized to simulate IL-6 concentrations over time under various step-up dosing scenarios. Based on the simulations, a modified step-up dosing regimen was proposed, consisting of an initial dose of 0.7

mg (split as 0.2 mg on cycle 1 day 1 and 0.5 mg on cycle 1 day 2), an intermediate dose 1 of 4 mg (split as 2 mg on cycle 1 day 8 and 2 mg on cycle 1 day 9), and an intermediate dose 2 of 20 mg (split as 10 mg on cycle 1 day 15 and 10 mg on cycle 1 day 16) (ie, the 0.7/4/20 regimen).

Based on the totality of information (clinical CRS data, odronextamab concentrations, IL-6 concentrations, and the QSP model-based assessment), a new step-up dosing regimen of 0.7/4/20 mg in cycle 1, along with an intensified premedication schedule, was recommended to be tested in the FL, DLBCL, and other B-NHL cohorts. Thus, the 0.7/4/20 mg regimen was subsequently implemented in Study 1625 and Study 1333.

2.6.5.1.1. FL

The full doses for the treatment of FL (80 mg QW/160 mg Q2W followed by 160 mg Q4W) were selected based on integrated safety, efficacy, and PK analyses obtained from Study 1333.

According to the applicant, an initial analysis based on data from Study 1333 showed an exposure-response relationship; ORR in patients with FL increased with odronextamab exposure; a 96% probability for achieving ORR was estimated at the median C_{trough} at week 12 of the 80 mg QW dose. This analysis is consistent with the review of efficacy data from Study 1333 showing a similar efficacy profile for doses between 80 mg and 320 mg QW. These data informed the selection of 80 mg QW doses for the treatment of FL in cycles 2 through 4.

PK analysis in Study 1333 indicated that, with a 160 mg Q2W regimen, C_{trough} of odronextamab is similar to those achieved with 80 mg QW in cycles 2 to 4, supporting the selection of 160 mg Q2W for maintenance. According to the applicant, this offers an advantage to patients, as reduced dosing frequency is less burdensome. Therefore, the 80 mg QW/160 mg Q2W regimen was selected for the treatment of FL.

In Study 1625 and Study 1333 (dose expansion), patients who had sustained CR were eligible to receive 160 mg Q4W as the residual tumour burden and resulting target-mediated drug clearance were expected to be substantially lower than at the start of study treatment, and thus the transition to less frequent odronextamab dosing was thought to be justified in these patients. According to the applicant, PK data demonstrate that trough drug concentration with the 160 mg Q4W regimen is above the threshold considered necessary to maintain efficacy. In addition, the reduction in the frequency of infusions from Q2W to Q4W is expected to improve patient convenience and did not result in increased risk of CRS or disease progression, as reported by the applicant. Thus, 160 mg Q4W was proposed for investigation in Study 1625 and Study 1333 in FL patients with CR for at least 9 months, to evaluate its effect on CR maintenance.

2.6.5.1.2. DLBCL

The full doses for the treatment of DLBCL (160 mg QW/320 mg Q2W followed by 320 mg Q4W) were selected based on integrated safety, efficacy, and PK analyses obtained from Study 1333.

According to the applicant, an initial analysis based on data from Study 1333 showed an exposure-response relationship; ORR increased with odronextamab exposure. A near maximum, 56% probability for achieving ORR, was estimated at exposures consistent with the median C_{trough} of 160 mg QW dose at week 12.

In addition, as reported by the applicant, review of preliminary efficacy data of 160 mg QW and 320 mg QW cohorts from the randomized portion of Study 1625 showed similar ORR in the 2 cohorts, supporting the selection of 160 mg QW doses for the treatment of DLBCL in cycles 2 through 4.

PK analyses in Study 1333 indicated that, with a 320 mg Q2W maintenance regimen, the C_{trough} of odronextamab was similar (or greater) to that achieved with the 160 mg QW regimen during cycles 2-4. According to the applicant, the Q2W regimen offers an advantage to patients, as reduced dosing frequency is less burdensome. Therefore, the 160 mg QW/320 mg Q2W regimen was selected for the treatment of DLBCL.

In Study 1625 and Study 1333 (dose expansion), patients who had sustained CR for at least 9 months were eligible to receive 320 mg Q4W. According to the applicant, PK data demonstrate that trough drug concentration with the 320 mg Q4W regimen is above the threshold considered necessary to maintain efficacy. In addition, the reduction in the frequency of infusions from Q2W to Q4W is expected to improve patient convenience and did not result in increased risk of CRS or disease progression, as reported by the applicant. Thus, 320 mg Q4W was proposed for investigation in Studies 1625 and 1333 in DLBCL patients with CR for at least 9 months, to evaluate its effect on longer-term CR maintenance.

2.6.5.2. Main study(ies)

Study 1625 – pivotal for FL and DLBCL

Study 1625 is an ongoing open-label, single-arm, multi-center, phase 2 study of odronextamab in patients with 5 disease-specific B-NHL cohorts: FL, DLBCL, MCL, MZL, and other B-NHL (containing aggressive B-NHL subtypes not included in the other 4 cohorts) that have relapsed after or are refractory to prior systemic therapy.

Methods

Study Participants

Key eligibility criteria for all patients in study 1625

- Age ≥18 years with r/r NHL
- Performance status (PS) 0-1
- Refractory was defined as no response (stable disease/PD) or relapse within ≤6 months of last treatment. Relapse was defined as disease that recurred following a response lasting >6 months from completion of the last dose of any line of therapy.
- In the judgment of the investigator, require systemic therapy for lymphoma at the time of study enrollment.
- Patients must have had prior treatment with an anti-CD20 antibody therapy.
- Adequate bone marrow function with platelet count ≥50 x 109/L, hemoglobin ≥9.0 g/dL, absolute neutrophil count (ANC) ≥1.0 x 109/L.

Key exclusion criteria for all patients in study 1625

- Prior treatment with any CAR-T therapy
- Prior allogeneic stem cell transplantation
- Prior treatment with an anti-CD20 x anti-CD3 bispecific therapy

- Continuous systemic corticosteroid treatment with more than 10 mg per day of prednisone or anti-inflammatory equivalent within 72 hours of start of study drug.
- Primary central nervous system (CNS) lymphoma or known involvement by non-primary CNS NHL
- Cardiac ejection fraction <40%
- Any infection requiring hospitalization or treatment with IV anti-infectives within 2 weeks of first administration of study drug.
- Uncontrolled infection with human immunodeficiency virus (HIV), hepatitis B or hepatitis C infection; or other uncontrolled infection, including cytomegalovirus (CMV) infection as noted by detectable levels on a blood PCR assay – patients who show detectable levels of CMV at screening will need to be treated with appropriate antiviral therapy and demonstrate at least 2 undetectable levels of CMV by PCR assay (at least 7 days apart) before being reconsidered for eligibility.

Key eligibility criteria unique for patients with FL were as follows:

- Patients with FL grade 1-3a that relapsed after or was refractory to at least 2 prior lines of systemic therapy, including an anti-CD20 antibody and an alkylating agent; patients must have failed combination lenalidomide and rituximab treatment where approved or deemed not appropriate to receive this treatment according to the investigator.
- Central histopathologic confirmation of the FL grade 1-3a diagnosis must have been obtained before study enrollment, according to WHO classification (Swerdlow, 2017).

Key eligibility criteria unique for patients with DLBCL were as follows:

- Patients with DLBCL that relapsed after or was refractory to at least 2 prior lines of systemic therapy, including an anti-CD20 antibody and an alkylating agent.
- Patients with de novo DLBCL or DLBCL that was transformed from a lower grade neoplasm (eg, FL or CLL) could be enrolled. Patients with DLBCL transformation from prior CLL could only be enrolled in the absence of a leukemic CLL component. For patients with transformed DLBCL, prior systemic therapies administered for the lower grade neoplasm were not to be considered among the prior lines of therapy for the purpose of determining eligibility.

  The following subtypes based on the WHO classification (Beham-Schmid, 2017) were eligible:

  DLBCL NOS;

  - Germinal center B-cell type (GCB type)

  - Activated B-cell type (ABC type)

Confirmed CD20 positivity at enrollment was not an inclusion criterion, despite the mechanism of action with a bispecific CD20/CD3 antibody as odronextamab.

According to the inclusion criteria, DLBCL NOS - GCB type/ABC type were the eligible subtypes (WHO 2017) in study 1625. However, some patients in the DLBCL cohort were identified with gene rearrangements (and by that HGBL diagnosis) after enrollment.

The subtype "Transformations of indolent B-cell lymphomas" has recently been implemented in the 5th WHO classification of 2022 (under the category Mature B-cells neoplasms) but has previously not been specified in the WHO classification. In SmPC section 5.1, the applicant has specified that lymphoma

classification in study 1625 was based on WHO classification 2017, i.e., the revised 4th edition, for both FL and DLBCL.

Treatments

Odronextamab was administered IV, first in 4 cycles (each cycle was 21-day) and then in a maintenance phase with Q2W dosing.

If a patient had maintained CR for 9 months, then odronextamab was to be administered every 4 weeks at the same dose.

Odronextamab was given until disease progression or other protocol defined reason for treatment discontinuation.

Initially, odronextamab was administered with a step-up regimen of 1/20 mg (the "1/20 regimen") during cycle 1 to mitigate for CRS. However, after global Protocol Amendment 3, the step-up regimen was modified to 0.7/4/20 mg (the "0.7/4/20 regimen"), to address the observed rates of grade 3 CRS. Please refer to section Dose response study(ies) for details on the rationale for selected step-up regimens.

Thus, patients in study 1625, and also study 1333, were enrolled under both the 1/20 regimen and 0.7/4/20 regimen.

Premedication (according to protocol amendment 5)

The following premedication was applied from the initial dose through the first QW dose as a single infusion (i.e., from cycle 1 day 1 until cycle 2 day 1).

- 12-24 hours prior to planned start of infusion
    - Dexamethasone 10 mg orally (PO) or equivalent dose of steroid
- Premedication on each day of infusion
    - Dexamethasone 20 mg IV 1 to 3 hours prior to start of infusion
    - Diphenhydramine 25 mg IV or PO 30 to 60 min before
    - Paracetamol 650 mg PO 30 to 60 min before
- 24 (±4) hours from the end of infusion
    - Dexamethasone 10 mg PO or equivalent dose of steroid

The following premedication was applied from the first dose following QW full dose (i.e., from cycle 2 day 8)

- Dexamethasone 10 mg IV 1 to 3 hours prior to start of infusion
- Diphenhydramine 25 mg IV or PO 30 to 60 min before
- Paracetamol 650 mg PO 30 to 60 min before

For subsequent doses no premedication was required if the previous single infusion was tolerated without experiencing an IRR and/ or CRS of any grade.

Concomitant medication (according to protocol amendment 5)

During the treatment period, patients should not receive any treatment of their malignancy (including chemotherapy, radiation, immune therapy, other experimental therapies) other than odronextamab.

Ongoing systemic corticosteroid treatment of more than 10 mg per day of prednisone or anti-inflammatory was prohibited.

Because treatment with odronextamab is expected to lead to B cell depletion, prophylaxis medications were recommended as follows for the specified groups:

- All patients – PJP prophylaxis
- Patients with IgG levels <400 mg/dL and for patients with recurrent infections with IgG between 400 and 600 mg/dL – receive IVIG.
- Patients with positive HbsAg, hepatitis B core antibody, and/or measurable viral load – receive hepatitis B virus prophylaxis.
- Patients with prior CMV/HSV infections – receive CMV/HSV prophylaxis.

See tables below for evaluated doses and treatment schedule for (i) FL and (ii) DLBCL in study 1625.

Table 8 Odronextamab dose and schedule in study 1625 for the treatment of R/R FL

Day of Treatment Cycle		Dose of IV Odronextamab (mg)	
		0.7/4/20 regimen (Proposed for registration)	1/20 regimen
Cycle 1 (Step Up)	Day 1	0.2	0.5
	Day 2	0.5	0.5
	Day 8	2	10
	Day 9	2	10
	Day 15	10	80
	Day 16	10	-
Cycle 2 to 4	Day 1	80	80
	Day 8	80	80
	Day 15	80	80
Maintenance (every 2 weeks)	Begin 1 week after end of Cycle 4	160	160

initial dose will be 0.7 mg split as 0.2 mg on cycle 1 day 1 and 0.5 mg on cycle 1 day 2; intermediate dose 1 will be 4 mg (split as 2 mg on cycle 1 day 8 and 2 mg on cycle 1 day 9); intermediate dose 2 will be 20 mg (split as 10 mg on cycle 1 day 15 and 10 mg on cycle 1 day 16).
Note: If a patient has maintained CR for 9 months, then odronextamab will be administered every 4 weeks at the same dose.

Table 9 Odronextamab dose and schedule in study 1625 for DLBCL

Day of Treatment Cycle		Dose of IV Odronextamab (mg)	
		0.7/4/20 regimen (Proposed for registration)	1/20 regimen
Cycle 1 (Step Up)	Day 1	0.2	0.5
	Day 2	0.5	0.5
	Day 8	2	10
	Day 9	2	10
	Day 15	10	160
	Day 16	10	-
Cycles 2-4	Day 1	160	160
	Day 8	160	160
	Day 15	160	160
Maintenance (Every 2 Weeks)	Begin 1 week after end of Cycle 4	320	320

Initial dose will be 0.7 mg split as 0.2 mg on cycle 1 day 1 and 0.5 mg on cycle 1 day 2; intermediate dose 1 will be 4 mg (split as 2 mg on cycle 1 day 8 and 2 mg on cycle 1 day 9); intermediate dose 2 will be 20 mg (split as 10 mg on cycle 1 day 15 and 10 mg on cycle 1 day 16)
Note: If a patient has maintained CR for 9 months, then odronextamab will be administered every 4 weeks at the same dose.

Objectives

Primary objective

According to protocol amendment 5, the primary objective of study 1625 is to assess the anti-tumour activity of single agent odronextamab as measured by ORR according to the Lugano Classification (Cheson, 2014) in each the following non-Hodgkin lymphoma (B-NHL) subgroups:

- FL grade 1-3a that has relapsed after or is refractory to at least 2 prior lines of systemic therapy, including an anti-CD20 antibody and an alkylating agent.
- DLBCL that has relapsed after or is refractory to at least 2 prior lines of systemic therapy, including an anti-CD20 antibody and an alkylating agent.
- Mantle cell lymphoma (MCL) that has relapsed after or is refractory to a Bruton's tyrosine kinase (BTK) inhibitor.
- Marginal zone lymphoma (MZL) that has relapsed after or is refractory to at least 2 prior lines of systemic therapy.
- Other B-NHL subtypes that have relapsed after or are refractory to at least 2 prior lines of systemic therapy.

For **FL**, a prespecified ORR of 49% was chosen by the applicant as the minimum clinically meaningful ORR for the FL cohort, in the SAP.

For **DLBCL**, a prespecified ORR of 35% was chosen by the applicant as the minimum clinically meaningful ORR for the DLBCL cohort, in the SAP.

Outcomes/endpoints

Primary endpoint

According to protocol amendment 5, the primary endpoint of the study for each of the five disease-specific cohort is as follows:

- ORR according to the Lugano Classification of response in malignant lymphoma (Cheson, 2014) and as assessed by independent central review. The ORR is assessed from the time of the first patient first dose until all patients have completed 52-week tumour assessment for FL grade 1-3a/MZL and 36-week tumour assessment for DLBCL/MCL/Other B-NHL or have withdrawn from the study.

Secondary endpoints

The secondary endpoints of the study for each of the five disease-specific cohorts included:

- ORR according to the Lugano Classification and as assessed by local investigator evaluation.
- Complete response (CR) rate according to the Lugano Classification and as assessed by local investigator evaluation and independent central review.
- PFS according to the Lugano Classification and as assessed by independent central review, and local investigator evaluation.
- OS is assessed from the time of the first patient first dose until the end of the study.
- DoR according to the Lugano Classification and as assessed by independent central review, and local investigator evaluation.

Schedule for response assessment

- CT/MRI imaging:

CT (unless contraindicated) or MRI is required during screening, at week 12, and then approximately Q8W up to week 52 in first year, and Q12W up to week 100 in second year, and then reduced frequency according to Schedule of event table in study protocol. A CT scan Q24W was performed until progression, start of non-protocol anti-lymphoma therapy or at any time when disease progression is suspected.

- FDG-PET imaging:

FDG-PET will be performed at screening. If positive at screening FDG-PET will be performed at week 12, at week 20 (if CR is not observed at week 12), and week 36 in year 1. FDG-PET will then be performed once each at the end of years 2 and annually thereafter at a time point that coincides with the planned CT or MRI tumour assessment. FDG-PET must be repeated in patients with FDG-avid disease to confirm response. Any suspected CR should be confirmed by FDG-PET scan. If the patient discontinued treatment due to reasons other than clinical or radiologic PD, disease assessments will continue to be performed until PD according to the follow-up period in the protocol. If FDG-PET is negative at screening, it does not need to be repeated.

- Bone marrow aspirate (BMA) and/or bone marrow biopsy (BMBx)

Bone marrow aspirate (BMA) and/or bone marrow biopsy (BMBx) will be performed during screening, at week 12, if patient has a CR to confirm response; and if progression is suspected. All bone marrow evaluations after screening will be required only if evidence of bone marrow disease is present at baseline.

Overall, the objectives and endpoints are considered appropriate for a phase 2 single-arm trial, and of clinical relevance.

Sample size

The sample size was determined to preserve adequate probability of observing 95% CI lower bound excluding the minimum clinically meaningful ORR for each disease-specific cohort. A single-stage exact binomial design was adopted for the primary endpoint of ORR.

For the **FL cohort**, assuming that an ORR of greater than 49% is clinically meaningful; with 112 patients, an ORR of at least 59% will have a lower bound of the confidence interval that excludes 49%. The enrollment in this cohort continued beyond 112 patients in order to have at least 60 patients treated with the revised step-up regimen.

For **DLBCL cohort**, as an initial step, 68 patients were randomized into the two treatment arms with 1:1 ratio (Arm 1: 160 mg QW dosing followed by 320 mg Q2W dosing; Arm 2: 320 mg QW dosing followed by 320 mg Q2W dosing). Data from the initial step was to be used for descriptive analyses that support PK/pharmacodynamic and advance understanding of the exposure-response relationship.

After the initial step, enrollment was only continued in the 160 mg QW/320 mg Q2W arm until a total of 112 patients (up to approximately 127 patients including the randomized patients in the arm) were reached to further study efficacy at this selected dose regimen. Assuming a clinical meaningful ORR is greater than 35%, with 112 patients, an ORR of at least 45% will have a lower bound of the confidence interval that excludes 35%. The enrolment in this cohort continued beyond 112 patients in order to have at least 60 patients of DLBCL or Other B-NHLs (minimum 45 DLBCL patients) treated with the new step-up regimen.

Randomisation and blinding (masking)

The study is single-arm in all cohorts except for DLBCL cohort where in an initial step, 68 patients were randomized into the two treatment arms with 1:1 ratio:

- Arm 1: 160 mg QW dosing followed by 320 mg Q2W dosing,
- Arm 2: 320 mg QW dosing followed by 320 mg Q2W dosing.

Following the initial randomization step, patients in the DLBCL cohort were to be assigned to the 160 mg QW/320 mg Q2W dose regimen.

Statistical methods

No formal statistical testing was planned for this study due to no comparator arm in the study. All analyses are descriptive in nature and summarized by disease-specific cohort. Confidence intervals were reported at the two-sided 95% level. In efficacy analysis of ongoing data, the patients who had opportunity for 12 weeks efficacy assessment were included.

The CSR presents the interim efficacy analysis for 2 global cohorts: patients with FL grade 1-3a and the primary analysis for patients with DLBCL.

Table 10 Efficacy Endpoints in Study 1625 Interim CSR by Cohort

Cohort	Type of Analysis	Endpoints
FL Grade 1-3a	Interim (prespecified) When 80 patients with FL grade 1-3a had completed 52-week assessment or withdrew from the study earlier	ORR[a], CR[a], PFS[a], OS, DOR[a], DOCR[a], DOPR[a], DCR[a], TTR[a], TTCR[a], time to new anti-lymphoma therapy, sensitivity analyses (DOR[a], DOCR[a], OS, and PFS[a]), and PROs (EORTC QLQ C30, FACT-Lym, and EQ-5D-3L)
DLBCL	Primary When 127 patients with DLBCL had completed 36-week assessment or withdrew from the study earlier	

[a] Assessed by IRC and investigator
CR, Complete response; DCR, Disease control rate; DLBCL, Diffuse large B-cell lymphoma; DOCR, Duration of complete response; DOR, Duration of response; DOPR, Duration of partial response; EORTC-QL-QC30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D-3L, 3-Level EQ-5D; FACT-Lym, Functional Assessment of Cancer Therapy-Lymphoma; FL, Follicular lymphoma; IRC, Independent central review; ORR, Objective response rate; OS, Overall survival; PFS, Progression-free survival; TTCR, Time to complete response; TTR, Time to response.
Note: Efficacy analyses are presented in this CSR for the FL grade 1-3a and DLBCL global cohorts. Global cohorts consist of the patient population excluding the regional extension cohorts in Japan and China.

Analysis populations

Full analysis set (FAS) includes all enrolled patients who received any doses of odronextamab. Efficacy and baseline variables were to be analysed using the FAS.

The safety analysis set (SAF) includes all patients who received any dose of odronextamab. Treatment compliance/administration and all clinical safety variables were analysed using the SAF.

The Efficacy Analysis Set included all enrolled patients who received any dose of odronextamab and had the opportunity for efficacy assessment at 12 weeks. The 12-week (±7 days) window is defined from day 77 to day 91 (inclusive). To be considered as having an opportunity for efficacy assessment at 12 weeks, a patient must meet one of the following conditions:

- Started study treatment >91 days prior to the data cutoff, or
- Started study treatment between 77 days and 91 days (inclusive) prior to the data cutoff and had an efficacy assessment in this period, died, discontinued the study, or discontinued treatment due to progression, withdrawal of consent, or lost to follow-up any time.

A patient who started study treatment <77 days prior to data cutoff is not considered as having an opportunity for efficacy assessment at 12 weeks.

Primary analysis

The primary efficacy endpoint was Objective response rate (ORR) according to Lugano Classification per IRC. Estimates of response rate, along with its exact two-sided 95% CI by Clopper and Pearson were presented.

The final analysis for primary efficacy endpoint was to be performed after the patients have completed 52 weeks tumour assessments in FL/MZL, 36 weeks tumour assessment in DLBCL/MCL/Other B-NHL or have withdrawn from the study earlier.

Descriptive analysis for patients in the two regimen arms (160 mg QW/320 mg Q2W, 320 mg QW/320 mg Q2W) in DLBCL cohort was to be performed to support PK/pharmacodynamic and advance the understanding of the exposure-response analysis.

Subgroup analyses were prespecified by baseline and demographic characteristics.

Secondary analyses

Similar method as described for the primary endpoint ORR was used for analyses of following secondary response endpoints: ORR per investigator, CR and Disease control rate (DCR).

Survival analysis was performed for secondary endpoints: progression-free survival (PFS), overall survival (OS), duration of response (DoR), duration of complete response (DOCR), Duration of partial response (DOPR), and time to response (TTR).

Survival curves were estimated using the Kaplan Meier (KM) product limit method and presented graphically. A two-sided 95% CI for median survival was calculated. Survival rates at fixed time points (6 months, 12 months, 18 months, etc.) were presented along with their corresponding 95% CIs.

Other secondary endpoints were analysed using descriptive statistics.

Interim efficacy analysis

An interim efficacy analysis for primary efficacy endpoint was to be performed when 80 patients with FL grade 1-3a have completed 52-week assessment and all patients in the DLBCL cohort have completed 36-week assessment or have withdrawn from the study, whichever is later.

Interim futility analysis

An interim futility analysis was planned for each of the MCL, MZL, and other B-NHL disease-specific cohorts after the pre-specified number of evaluable patients in the cohort have completed tumour assessments at 28 weeks or have withdrawn from the study earlier. The futility boundary was determined based on lack of clinically meaningful activity below the threshold in each disease-specific cohort.

Multiplicity

Since no formal statistical testing is planned in this study, adjustment for multiplicity is not relevant.

Safety data monitoring

An Independent Data Monitoring Committee (IDMC) composed of members who are independent from the sponsor and the study sites, was to be established to conduct formal reviews of accumulated clinical data.

SAP management

Only one SAP version is authored. It is dated 17 December 2021, with the approval signatures on 22 February 2022 and 1 March 2022. (Data cutoff for the interim analysis was 31 January 2023, and the database lock on 23 March 2023.)

A separate analysis plan was prepared for evaluation of patient-reported outcomes (PROs). It describes longitudinal analysis of PROs and methods to determine clinically meaningful thresholds to be used in the PRO responder analysis.

Changes in planned analysis

There were changes to the CSR analysis following the final version of the SAP:

- Per Lugano, BOR of stable disease does not require ≥12 weeks after start of study drug. Therefore, ≥12 weeks requirement was not applied to the CSR analysis, which is different than the method specified in the SAP.

• The Efficacy Analysis Set was clarified as a specific set (not the same as the FAS).
• Periods 1 and 2 were defined as a way to facilitate the understanding of CRS and other cytokine-driven AEs.

The Summary of Treatment-Related ICANS per Sponsor Definition, originally planned by the sponsor, is not included in the CSR.

Results

- **Participant flow**

FL

Patient disposition for **FL** by step-up regimen by DCO 31 Jan 2023 is summarized in table below.

Table 11 Patient disposition FL by DCO 31 Jan 2023

Table 2: Patient Disposition – Patients with FL Grade 1-3a (Full Analysis Set)

	FL Grade 1-3a 1/20/80 mg (N=68)	FL Grade 1-3a 0.7/4/20/80 mg (N=72)	Total (N=140)
Treatment Ongoing, n (%)	9 (13.2%)	42 (58.3%)	51 (36.4%)
Treatment Discontinued, n (%)	59 (86.8%)	30 (41.7%)	89 (63.6%)
Primary Reason for Treatment Discontinuation			
ADVERSE EVENT	11 (16.2%)	7 (9.7%)	18 (12.9%)
DEATH	10 (14.7%)	4 (5.6%)	14 (10.0%)
SPONSOR REQUEST	0	0	0
PHYSICIAN DECISION	10 (14.7%)	1 (1.4%)	11 (7.9%)
PROGRESSIVE DISEASE	19 (27.9%)	11 (15.3%)	30 (21.4%)
WITHDRAWAL BY SUBJECT	6 (8.8%)	3 (4.2%)	9 (6.4%)
WITHDRAWAL OF CONSENT	2 (2.9%)	4 (5.6%)	6 (4.3%)
OTHER	1 (1.5%)	0	1 (0.7%)

FL, Follicular lymphoma
Source: Module 5.3.5.2 R1979-ONC-1625 Interim CSR Table 6, PTT 14.1.1.5.so, 14.1.1.5.sr.

The Applicant has provided a Consort diagram by updated DCO 20 Oct 2023 to illustrate the transition from Q2W to Q4W in patients that remained in CR for 9 months, by step-up regimen, see below.

Figure 5: Consort Diagram for FL Patients by Step-up Regimen

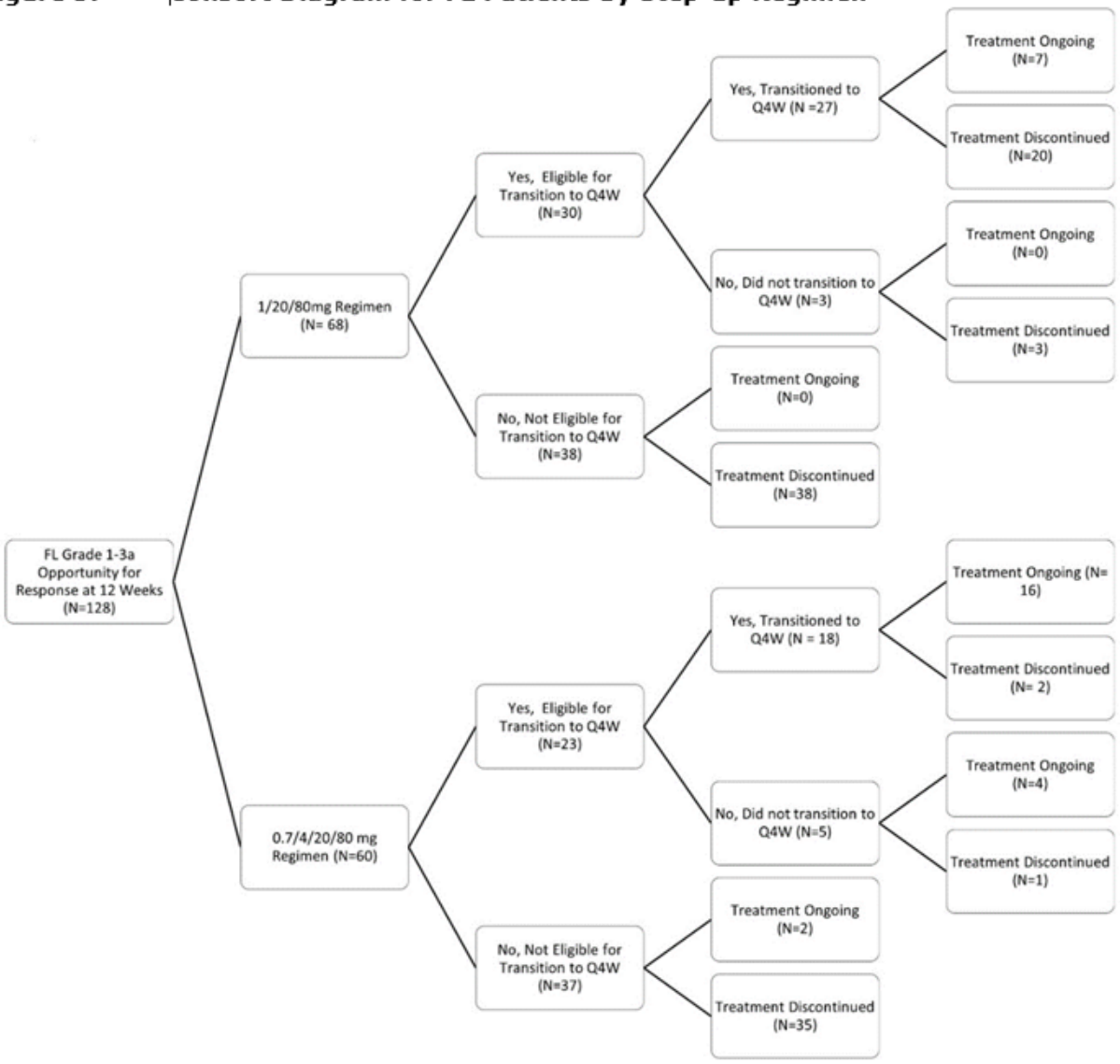


Figure 7 Consort diagram for FL by step-up regimen by updated DCO 20 Oct 2023

Most patients that were eligible for transition from Q2W to Q4W also did the transition. Reasons for not doing the transition included dose delays due to AE that required subsequent dose resumption with step-up dosing and suspicion of progressive disease at the timepoint for transition.

Of the 45 patients with FL who transitioned to Q4W, 9 patients had PD after the transition. The applicant has clarified that none of the PD events in FL patients (global cohort FAS) occurred during step-up dosing, for either step-up regimen, which is considered reassuring with regard to homogeneity in response between the step-up regimens.

DLBCL

Patient disposition for **DLBCL** by step-up regimen by DCO 31 Jan 2023 is summarized in table below.

Table 12 Patient disposition DLBCL by DCO 31 Jan 2023

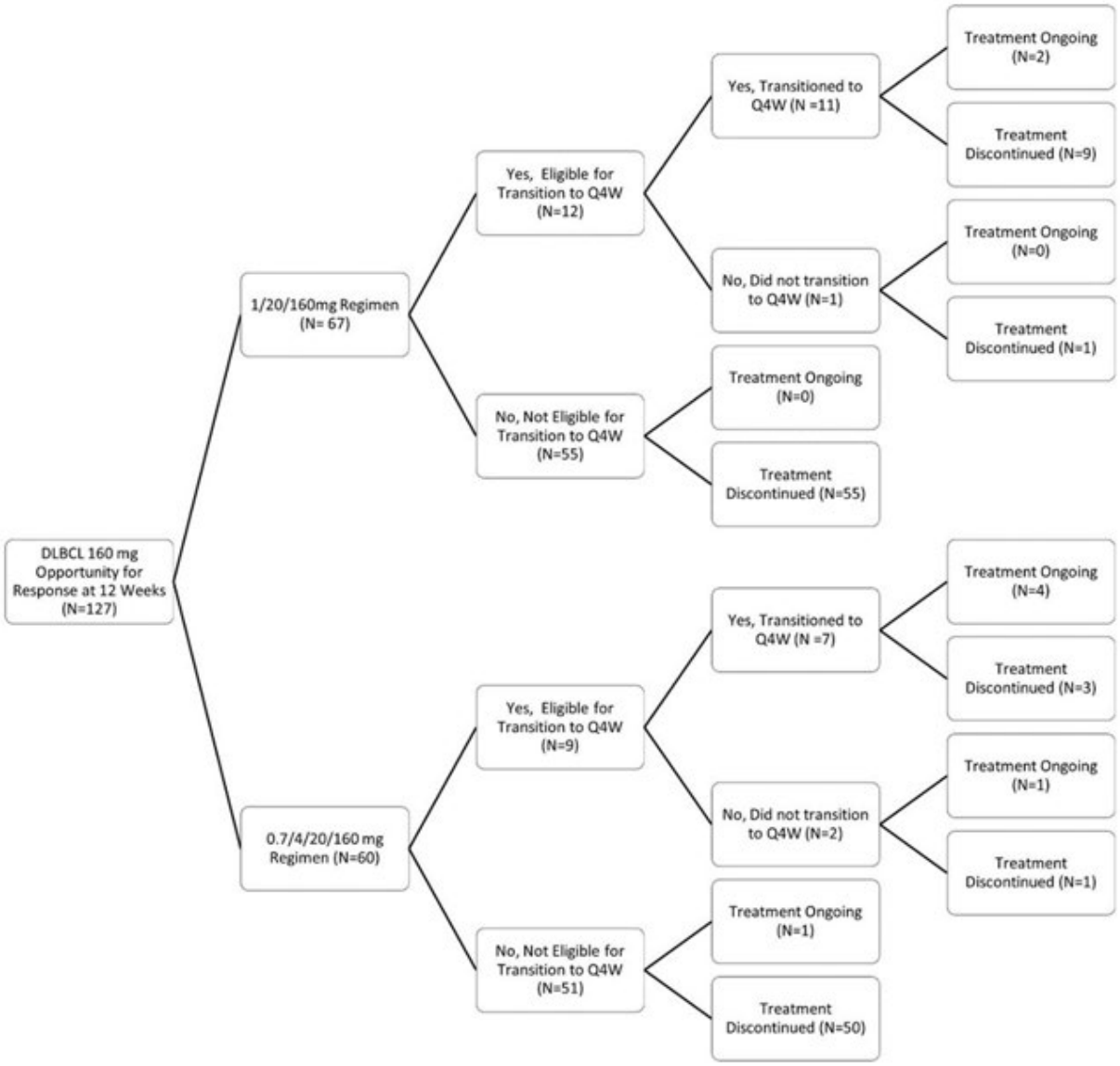
Table 3: R1979-ONC-1625 Patient Disposition – Patients with DLBCL 160 mg Cohort by Step-up Regimen (Full Analysis Set)

	DLBCL 1/20/160 mg (N=67)	DLBCL 0.7/4/20/160 mg (N=74)	Total (N=141)
Treatment Ongoing, n (%)	6 (9.0%)	15 (20.3%)	21 (14.9%)
Treatment Discontinued, n (%)	61 (91.0%)	59 (79.7%)	120 (85.1%)
Primary Reason for Treatment Discontinuation			
ADVERSE EVENT	9 (13.4%)	9 (12.2%)	18 (12.8%)
DEATH	8 (11.9%)	13 (17.6%)	21 (14.9%)
PHYSICIAN DECISION	5 (7.5%)	3 (4.1%)	8 (5.7%)
PROGRESSIVE DISEASE	32 (47.8%)	29 (39.2%)	61 (43.3%)
WITHDRAWAL BY SUBJECT	1 (1.5%)	2 (2.7%)	3 (2.1%)
WITHDRAWAL OF CONSENT	6 (9.0%)	3 (4.1%)	9 (6.4%)

Data cutoff: 31 Jan 2023
DLBCL, diffuse large B-cell lymphoma.
Source: Module 5.3.5.2 R1979-ONC-1625 Interim CSR PTT 14.1.1.5.so, 14.1.1.5.sr, 14.1.1.5.sa

The Consort diagram below by updated DCO 20 Oct 2023 illustrates the transition from Q2W to Q4W in patients that remained in CR for 9 months, by step-up regimen, see below.

Figure 8 Consort diagram for DLBCL by step-up regimen by updated DCO 20 Oct 2023



As also seen in the FL cohort, most DLBCL patients that were eligible for transition from Q2W to Q4W also did the transition.

Of the 18 DLBCL patients who transitioned to Q4W, 3 patients had PD after the transition

It is noted that a numerically slightly higher proportion of DLBCL patients discontinued odronextamab prior to reaching full dose due to progressive disease in the 0.7/4/20 vs 1/20 and mg step-up regimen cohorts. However, the notably limited sample size (7 of 74 subjects in the 0.7/4/20 mg cohort and 5 of 67 subjects in the 1/20 mg cohort, from the FAS with all enrolled subjects) makes it difficult to draw firm conclusions on these data.

FL and DLBCL

The Applicant provided an updated table for Participant flow (updated DCO 20 Oct 2023) for the efficacy analysis set of FL (n=128) and DLBCL (n=127) together with the other 3 cohorts in study 1625, see below.

Table 13 Participant flow in study 1625 by updated DCO 20 Oct 2023

Table 6: Patient Disposition (Efficacy Analysis Set)
B-NHL Patients by Subtype and Dose

	FL Grade 1-3a 80 mg (N=128)	MZL 80 mg (N=22)	MCL 160 mg (N=14)	Other B-NHL 160 mg (N=38)	DLBCL 160 mg (N=127)	DLBCL 320 mg (N=33)	Total (N=362)
Treatment Ongoing, n (%)	29 (22.7%)	4 (18.2%)	2 (14.3%)	10 (26.3%)	8 (6.3%)	0	53 (14.6%)
Treatment Discontinued, n (%)	99 (77.3%)	18 (81.8%)	12 (85.7%)	28 (73.7%)	119 (93.7%)	33 (100%)	309 (85.4%)
Primary Reason for Treatment Discontinuation							
ADVERSE EVENT	21 (16.4%)	5 (22.7%)	2 (14.3%)	3 (7.9%)	19 (15.0%)	7 (21.2%)	57 (15.7%)
DEATH	13 (10.2%)	0	2 (14.3%)	2 (5.3%)	21 (16.5%)	4 (12.1%)	42 (11.6%)
SPONSOR REQUEST	0	0	1 (7.1%)	0	0	0	1 (0.3%)
PHYSICIAN DECISION	13 (10.2%)	5 (22.7%)	2 (14.3%)	4 (10.5%)	10 (7.9%)	3 (9.1%)	37 (10.2%)
PROGRESSIVE DISEASE	32 (25.0%)	4 (18.2%)	3 (21.4%)	16 (42.1%)	60 (47.2%)	15 (45.5%)	130 (35.9%)
WITHDRAWAL BY SUBJECT	13 (10.2%)	2 (9.1%)	2 (14.3%)	3 (7.9%)	1 (0.8%)	1 (3.0%)	22 (6.1%)
WITHDRAWAL OF CONSENT	6 (4.7%)	2 (9.1%)	0	0	8 (6.3%)	3 (9.1%)	19 (5.2%)
OTHER	1 (0.8%)	0	0	0	0	0	1 (0.3%)

	FL Grade 1-3a 80 mg (N=128)	MZL 80 mg (N=22)	MCL 160 mg (N=14)	Other B-NHL 160 mg (N=38)	DLBCL 160 mg (N=127)	DLBCL 320 mg (N=33)	Total (N=362)
Study Ongoing, n (%)	54 (42.2%)	10 (45.5%)	4 (28.6%)	15 (39.5%)	17 (13.4%)	3 (9.1%)	103 (28.5%)
Study Discontinued, n (%)	74 (57.8%)	12 (54.5%)	10 (71.4%)	23 (60.5%)	110 (86.6%)	30 (90.9%)	259 (71.5%)
Primary Reason for Study Discontinuation							
ADVERSE EVENT	2 (1.6%)	1 (4.5%)	0	0	3 (2.4%)	0	6 (1.7%)
DEATH	18 (14.1%)	0	3 (21.4%)	4 (10.5%)	41 (32.3%)	10 (30.3%)	76 (21.0%)
LOST TO FOLLOW-UP	0	0	0	0	1 (0.8%)	0	1 (0.3%)
PHYSICIAN DECISION	4 (3.1%)	1 (4.5%)	1 (7.1%)	1 (2.6%)	2 (1.6%)	0	9 (2.5%)
PROGRESSIVE DISEASE	24 (18.8%)	2 (9.1%)	3 (21.4%)	12 (31.6%)	30 (23.6%)	8 (24.2%)	79 (21.8%)
WITHDRAWAL BY SUBJECT	4 (3.1%)	1 (4.5%)	0	1 (2.6%)	5 (3.9%)	1 (3.0%)	12 (3.3%)
WITHDRAWAL OF CONSENT	13 (10.2%)	6 (27.3%)	3 (21.4%)	4 (10.5%)	16 (12.6%)	7 (21.2%)	49 (13.5%)
OTHER	9 (7.0%)	1 (4.5%)	0	1 (2.6%)	12 (9.4%)	4 (12.1%)	27 (7.5%)

Data cut-off as of Oct 20th, 2023.

Recruitment

Study Initiation Date: 20 Nov 2019 (first patient first visit).

Data cutoff for the Interim analysis of FL cohort and for the Primary analysis of DLBCL cohort is 31 Jan 2023.

The interim CSR for study R1979-ONC-1625 (study 1625) provides data from first patient first visit (20 Nov 2019) to data cutoff date of 31 Jan 2023 from the study. As of the data cutoff date, the global cohorts for FL and DLBCL have completed enrollment. Global cohorts consist of the patient population excluding the regional extension cohorts in Japan and China.

As of Protocol Amendment 5, the study is continuing enrollment in the Other B-NHL global cohort, and the MCL and MZL global cohorts are not currently enrolling.

The study was conducted at 92 centres that enrolled participants in 14 countries in North America, Europe, and Asia-Pacific.

FL

- Last patient with FL was enrolled on the 1/20 regimen 09 Dec 2020.
- First patient first dose 0.7/4/20 regimen was 06 Sep 2021.

- Last patient with FL was enrolled on the 0.7/4/20 regimen 27 Jul 2022 (global FL cohort enrollment completed)

For FL, the median estimated duration of follow-up was 8.2 months (95% CI 7.0-8.6 and range 6.2:16.9) for the 0.7/4/20 regimen vs 26.1 months (95% CI 23.1-29.0 and range 25.7:37.5) for the 1/20 regimen (DCO 31 Jan 2023, Interim analysis)

DLBCL

- Last patient with DLBCL was enrolled on the 1/20 regimen 08 Dec 2020.
- First patient first dose DLBCL on 0.7/4/20 regimen was 18 Aug 2021.
- Last patient with DLBCL was enrolled on the 0.7/4/20 regimen 18 May 2022 (global DLBCL cohort enrollment completed).

For DLBCL, the median estimated duration of follow-up was 11.8 months (95% CI 9.0-14.9 and range 8.5:17.5 months) for the 0.7/4/20 mg regimen vs 26.7 months (95% CI 22.7-28.2 and range 25.8:34.3) for the 1/20 mg regimen (DCO 31 Jan 2023, Primary analysis).

Conduct of the study

Table 14 Overview of important events in study 1625

Table 1: Overview of Important Events in Study 1625

Timepoint	Study 1625 Event
19 Dec 2018	Original Clinical Study Protocol
04 Nov 2019	Global Protocol Amendment 1
18 Dec 2019	First patient first dose FL grade 1-3a (1/20 regimen)
17 Mar 2020	First patient first dose DLBCL (1/20 regimen)
19 Jun 2020	Global Protocol Amendment 2
10 Nov 2020	Partial clinical hold by FDA on MCL cohort
11 Nov 2020	Global Protocol Amendment 3
08 Dec 2020	Last patient with DLBCL enrolled on the 1/20 regimen
09 Dec 2020	Last patient with FL grade 1-3a enrolled on the 1/20 regimen
10 Dec 2020	Partial clinical hold by FDA on all clinical studies involving odronextamab, including all cohorts in Study 1625
13 May 2021	Partial clinical hold for all clinical studies involving odronextamab lifted by FDA. Enrollment resumed for FL grade 1-3a, DLBCL, and Other B-NHL cohorts.[a]
14 May 2021	Global Protocol Amendment 4
18 Aug 2021	First patient first dose DLBCL (0.7/4/20 regimen)
06 Sep 2021	First patient first dose FL grade 1-3a (0.7/4/20 regimen)
11 Apr 2022	Global Protocol Amendment 5
20 April 2022	Administrative review data cut off
18 May 2022	Global DLBCL cohort enrollment completed (ie, last patient with DLBCL enrolled on the 0.7/4/20 regimen)
16 June 2022	Administrative review database lock
27 Jul 2022	Global FL grade 1-3a cohort enrollment completed (ie, last patient with FL grade 1-3a enrolled on the 0.7/4/20 regimen)
31 Jan 2023	Data cutoff for interim analysis of FL grade 1-3a cohort and primary analysis of DLBCL cohort for the BLA
23 Mar 2023	Database lock for interim analysis of FL grade 1-3a cohort and primary analysis of DLBCL cohort for the BLA

[a] MCL and MZL remained on hold as of Global Protocol Amendment 5.
BLA, Biologic License Application; B-NHL, B-cell non-Hodgkin lymphoma; DLBCL, Diffuse large B-cell lymphoma; FDA, Food and Drug Administration; FL, Follicular lymphoma; MCL, Mantle cell lymphoma; MZL, Marginzal zone lymphoma.

In global amendment 1, treatment duration was revised to continue until progression or other protocol defined reasons. All patients with FL and DLBCL were enrolled after amendment 1 and have consequently received odronextamab until progression.

In global amendment 2, inclusion criterion for FL was upgraded to require patients to have failed combination lenalidomide and rituximab treatment, where approved, or have been deemed not appropriate to receive this treatment. Prior treatment with lenalidomide in combination with rituximab was not applicable for majority of patients in study 1625 due to rituximab refractoriness and the fact that this combination was not approved or available in several countries where study 1625 was conducted. In the SmPC section 5.1, it is specified that 13% of the patients had received prior lenalidomide in combination with rituximab.

Under global amendment 3, enrollment was paused due to a fatal CRS event in a MCL patient. Several CRS mitigation strategies were implemented in global amendment 4, including the revised step-up regimen 0.7/4/20 mg. Further, in global amendment 4, the sample size was updated to provide sufficient data from patients dosed with the 0.7/4/20 step-up dosing regimen. At least 60 more patients were be enrolled with the new step-up regimen in FL, and in DLBCL or other aggressive B-NHL (minimum 45 patients with DLBCL).

The original SAP is dated 17 December 2021 and was based on the global protocol amendment 4, prior to database lock 23 March 2023, and prior to an administrative review which was added with amendment 5 in April 2022. First patient first dose FL on 0.7/4/20 regimen was 06 Sep 2021. First patient first dose DLBCL on 0.7/4/20 regimen was 18 Aug 2021. Thus, the SAP was written about 3 months after start of inclusion of patients with the revised step-up regimen, please refer to section Statistical considerations for further discussions on this issue.

Protocol deviations

Table 15 Important Protocol deviations (Safety Analysis Set)

	FL Grade 1-3a 80 mg (N=140)	MZL 80 mg (N=19)	MCL 160 mg (N=14)	Other B-NHL 160 mg (N=28)	DLBCL 160 mg (N=141)	DLBCL 320 mg (N=33)	Total (N=375)
Number of important protocol deviations	63	14	6	6	36	5	130
Patients with any important protocol deviation, n (%)	38 (27.1%)	9 (47.4%)	4 (28.6%)	5 (17.9%)	30 (21.3%)	4 (12.1%)	90 (24.0%)
Type of important protocol deviations, n (%)							
ENTERED STUDY EVEN THOUGH ENTRY CRITERIA WAS NOT SATISFIED	4 (2.9%)	7 (36.8%)	2 (14.3%)	0	12 (8.5%)	2 (6.1%)	27 (7.2%)
INADEQUATE INFORMED CONSENT ADMINISTRATION	2 (1.4%)	0	0	0	5 (3.5%)	2 (6.1%)	9 (2.4%)
PROCEDURE NOT PERFORMED	15 (10.7%)	3 (15.8%)	2 (14.3%)	3 (10.7%)	5 (3.5%)	1 (3.0%)	29 (7.7%)
PROCEDURE PERFORMED OUTSIDE OF WINDOW	0	1 (5.3%)	1 (7.1%)	0	3 (2.1%)	0	5 (1.3%)
RECEIVED WRONG TREATMENT OR INCORRECT DOSE	13 (9.3%)	1 (5.3%)	0	0	6 (4.3%)	0	20 (5.3%)
SUBJECT DEVELOPED WITHDRAWAL CRITERIA BUT WAS NOT WITHDRAWN	8 (5.7%)	0	0	2 (7.1%)	3 (2.1%)	0	13 (3.5%)

B-NHL, B-cell non-Hodgkin lymphoma; DLBCL, Diffuse large B-cell lymphoma; FL, Follicular lymphoma; MCL, Mantle cell lymphoma; MZL, Marginal zone lymphoma.
Source: PTT 14.1.1.7.sa

FL

A total of 15 (10.7%) patients had procedures not performed, the most common procedure not performed was a CT or MRI (in 9 patients).

A total of 13 (9.3%) patients received the wrong treatment or incorrect dose; this included patient received incorrect dose administration (initial, intermediate, nominal QW, Q2W maintenance doses, as applicable) (n=12) and infusion was administered for <2 hours for doses from week 1 through week 4 or through the first nominal dose administered as a single infusion (n=1).

Furthermore, 8 patients had a protocol deviation for meeting treatment withdrawal criteria but were not withdrawn. All of these were for temporary discontinuation or interruption of study treatment.

Four patients had a protocol deviation of 'entered study even though criteria were not satisfied', which included adequate renal function (n=1), adequate bone marrow function documented by ANC ≥0.75 × 10^9/L (patient may not have received G-CSF within 2 days prior to first dose odronextamab) (n=2), adequate hepatic function (n=1), and ECOG not 0 or 1 (n=1).

DLBCL

Six patients had a protocol deviation of receiving incorrect dose (initial, intermediate, nominal QW, Q2W maintenance doses, as applicable).

Three patients had a protocol deviation for meeting treatment withdrawal criteria but were not withdrawn. All of these were for temporary discontinuation or interruption of study treatment.

Overall, the reported protocol deviations are not considered to impact the overall efficacy conclusions in the FL or DLBCL cohort.

- **Baseline data**

Table 16 **Selected demographics and baseline characteristics FL Grade 1-3a by DCO 31 Jan 2023**

	FL Grade 1-3a 1/20/80 mg (N=68)	FL Grade 1-3a 0.7/4/20/80 mg (N=60)	Total (N=128)
Age (years)			
N	68	60	128
Mean (SD)	59.4 (12.54)	61.0 (11.40)	60.1 (12.00)
Median	59.5	61.5	61.0
Min : Max	22 : 84	36 : 81	22 : 84
Age groups (years), n (%)			
<65	46 (67.6%)	33 (55.0%)	79 (61.7%)
≥65	22 (32.4%)	27 (45.0%)	49 (38.3%)
Sex, n (%)			
Male	35 (51.5%)	33 (55.0%)	68 (53.1%)
Female	33 (48.5%)	27 (45.0%)	60 (46.9%)
Race, n (%)			
WHITE	39 (57.4%)	40 (66.7%)	79 (61.7%)
ASIAN	15 (22.1%)	19 (31.7%)	34 (26.6%)
OTHER	1 (1.5%)	0	1 (0.8%)
UNKNOWN	2 (2.9%)	0	2 (1.6%)
NOT REPORTED[a]	11 (16.2%)	1 (1.7%)	12 (9.4%)
ECOG performance status, n (%)			
0	38 (55.9%)	27 (45.0%)	65 (50.8%)
1	29 (42.6%)	33 (55.0%)	62 (48.4%)
2	1 (1.5%)	0	1 (0.8%)
Geographic Region, n (%)			
North America	17 (25.0%)	24 (40.0%)	41 (32.0%)
Europe	38 (55.9%)	32 (53.3%)	70 (54.7%)
Asia-Pacific	13 (19.1%)	4 (6.7%)	17 (13.3%)
Rest of World	0	0	0

ECOG, Eastern Cooperative Oncology Group; FL, Follicular lymphoma; Q1, Quartile 1; Q3, Quartile 3; SD, Standard deviation

[a] "Not reported" is affected by local country regulations.

Source: Module 5.3.5.2 R1979-ONC-1625 Interim CSR Table 9, PTT 14.1.2.1.er, PTT 14.1.2.1.eo, 14.1.2.1.ea.

Table 17 Selected tumour characteristics FL Grade 1-3a by DCO 31 Jan 2023 Efficacy Analysis set

	FL Grade 1-3a 1/20/80 mg (N=68)	FL Grade 1-3a 0.7/4/20/80 mg (N=60)	Total (N=128)
Ann Arbor Stage at Study Entry, n(%)			
I-II	10 (14.7%)	9 (15.0%)	19 (14.8%)
III-IV	58 (85.3%)	51 (85.0%)	109 (85.2%)
Bulky Disease, n(%)			
Yes	10 (14.7%)	8 (13.3%)	18 (14.1%)
No	58 (85.3%)	52 (86.7%)	110 (85.9%)
Refractory/Relapse at Study Entry, n(%)			
Refractory	51 (75.0%)	41 (68.3%)	92 (71.9%)
Relapse	17 (25.0%)	18 (30.0%)	35 (27.3%)
Unknown	0	1 (1.7%)	1 (0.8%)
Number of prior lines, median (range)			
Median	3.0	2.0	3.0
Min : Max	2 : 8	2 : 13	2 : 13
Risk Factors for FLIPI 1 in FL grade 1-3a, n(%)			
Low (0-1)	11 (16.2%)	10 (16.7%)	21 (16.4%)
Intermediate (2)	18 (26.5%)	15 (25.0%)	33 (25.8%)
High (3-5)	39 (57.4%)	35 (58.3%)	74 (57.8%)
FL POD24 Status, n(%)			
Yes	35 (51.5%)	28 (46.7%)	63 (49.2%)
No	33 (48.5%)	32 (53.3%)	65 (50.8%)

CD, Cluster of differentiation; FAS, Full analysis set; FL, Follicular lymphoma; FLIPI, Follicular Lymphoma International Prognostic Index; ICD-O, International Classification of Diseases for Oncology; NA, not applicable; POD24, Progress of Disease within 2 years of diagnosis

Note: Refractory at the study entry is defined as disease that progressed during previous therapy or relapsed within 6 months from completion of last line of therapy. Relapse at the study entry is defined as disease that recurred following a response lasting >6 months from completion of last line of therapy; also includes those with unknown/NA best response who, however, progressed/recurred >6 months from completion of last line of therapy.

Source: Module 5.3.5.2 R1979-ONC-1625 Interim CSR PTT 14.1.2.2.ea, 14.1.2.2.eo, 14.1.2.2.er, PTT 14.1.3.1.ea, 14.1.3.1.eo, 14.1.3.1.er.

The baseline data reflect a r/r FL population after multiple systemic therapies (at least 2), which is in line with the sought indication.

Prior lymphoma-related treatment

Of the 128 patients in the EAS with FL, 59 (46.1%) patients were refractory to first line and 92 (71.9%) were refractory to last line of treatment.

Ninety-five (74.2%) patients were refractory to prior anti-CD20 antibody, and 54 (42.2%) were double refractory to anti-CD20 antibody and alkylating agent.

Among 140 patients in the FAS, a total of 17 (13.3%) patients had prior rituximab and lenalidomide treatment. Fourteen percent of patients had received a prior PI3K inhibitor.

A total of 39/128 (30.5%) patients in the EAS had prior autologous stem-cell transplant.

Exposure, by DCO 31 Jan 2023

The median duration of exposure of odronextamab was 46.07 weeks (range 2.0 to 157.0 weeks) among the 68 patients in the 1/20 regimen.

The median duration of exposure of odronextamab was 24.07 weeks (range 0.4 to 73.3 weeks) among the 72 patients in the 0.7/4/20 regimen.

The reported difference in median duration of exposure was expected since that the patients treated in the 1/20 regimen had participated in the study longer at the time of the data cut.

DLBCL

Table 18 Selected demographics and baseline characteristics DLBCL160 mg cohort by step up regimen - DCO 31 Jan 2023

	DLBCL 1/20/160 mg (N=67)	DLBCL 0.7/4/20/160 mg (N=60)	Total (N=127)
Age (years)			
n	67	60	127
Mean (SD)	63.3 (12.01)	65.3 (13.57)	64.3 (12.76)
Median	65.0	68.5	67.0
Q1 : Q3	53.0 : 72.0	59.0 : 75.0	55.0 : 74.0
Min : Max	29 : 88	24 : 85	24 : 88
Age groups (years), n (%)			
<65	33 (49.3%)	21 (35.0%)	54 (42.5%)
≥ 65	34 (50.7%)	39 (65.0%)	73 (57.5%)
Sex, n (%)			
Male	39 (58.2%)	37 (61.7%)	76 (59.8%)
Female	28 (41.8%)	23 (38.3%)	51 (40.2%)
Race, n (%)			
WHITE	29 (43.3%)	32 (53.3%)	61 (48.0%)
ASIAN	31 (46.3%)	22 (36.7%)	53 (41.7%)
OTHER	0	0	0
UNKNOWN	0	0	0
NOT REPORTED	7 (10.4%)	6 (10.0%)	13 (10.2%)
ECOG performance status, n (%)			
0	25 (37.3%)	16 (26.7%)	41 (32.3%)
1	42 (62.7%)	44 (73.3%)	86 (67.7%)
2	0	0	0
Geographic Region, n (%)			
North America	4 (6.0%)	7 (11.7%)	11 (8.7%)
Europe	26 (38.8%)	26 (43.3%)	52 (40.9%)
Asia-Pacific	37 (55.2%)	27 (45.0%)	64 (50.4%)
Rest of World	0	11 (20.4%)	11 (20.4%)

Data cutoff: 31 Jan 2023

[a] "Not reported" is affected by local country regulations.

DLBCL, diffuse large B-cell lymphoma; ECOG, eastern cooperative oncology group; Max, maximum; Min, minimum; Q1, quartile 1; Q3, quartile 3; SD, standard deviation.

Source: Module 5.3.5.2 R1979-ONC-1625 PTTs 14.1.2.1.er,14.1.2.1.eo, and 14.1.2.1.ea

Source SCE DLBCL section 2.1.1.1

Table 19 Selected tumour characteristics DLBCL by DCO 31 Jan 2023- Efficacy Analysis Set

	DLBCL 1/20/160 mg (N=67)	DLBCL 0.7/4/20/160 mg (N=60)	Total (N=127)
Ann Arbor Stage at Study Entry, n(%)			
I-II	15 (22.4%)	8 (13.3%)	23 (18.1%)
III-IV	52 (77.6%)	51 (85.0%)	103 (81.1%)
Missing		1 (1.7%)	1 (0.8%)
Bulky Disease, n(%)			
Yes	13 (19.4%)	15 (25.0%)	28 (22.0%)
No	54 (80.6%)	45 (75.0%)	99 (78.0%)
Refractory/Relapse at Study Entry, n(%)			
Refractory	58 (86.6%)	52 (86.7%)	110 (86.6%)
Relapse	9 (13.4%)	8 (13.3%)	17 (13.4%)
Number of prior lines			
Median	3.0	2.0	2.0
Min : Max	2 : 7	2 : 8	2 : 8
DLBCL cell of origin, n(%)			
Germinal Center B-Cell-like DLBCL	26 (38.8%)	17 (28.3%)	43 (33.9%)
Activated B-Cell-like DLBCL / Non-GCB	25 (37.3%)	31 (51.7%)	56 (44.1%)
Unclassified DLBCL	4 (6.0%)	0	4 (3.1%)
Missing	12 (17.9%)	12 (20.0%)	24 (18.9%)
DLBCL Subtype, n(%)			
DLBCL, denovo	45 (67.2%)	51 (85.0%)	96 (75.6%)
DLBCL, transformed (Richter)	5 (7.5%)	2 (3.3%)	7 (5.5%)
DLBCL, transformed (non-Richter)	17 (25.4%)	7 (11.7%)	24 (18.9%)

The baseline data reflect a r/r DLBCL population after multiple systemic therapies (at least 2), which is in line with the sought indication.

All 96 patients with DLBCL de novo had DLBCL NOS.

Based on the updated data from 20 October 2023 DCO, the number of HGBL patients in DLBCL 160 mg cohort was 11 (8.7%); this is composite of DLBCL, double-hit 5 (3.8%) and DLBCL, triple-hit 6 (4.7%). MYC translocation was required to be considered either a double hit or triple hit lymphoma. It is noted that testing for double-hit and triple-hit lymphoma was not done in 61 (48%) of the DLBCL patients in study 1625.

Prior lymphoma-related treatment

Of the 127 enrolled patients in the DLBCL 160 mg cohort, 70 (55.1%) were refractory to first line and 110 (86.6%) were refractory to last line of treatment.

Ninety-nine (78.0%) of patients were refractory to prior anti-CD20 antibody, and 82 (64.6%) were double refractory to anti-CD20 antibody and alkylating agent.

Twenty-two (17.3%) of the DLBCL patients had received prior autologous stem cell transplant.

Exposure, by DCO 31 Jan 2023

The median duration of exposure of odronextamab was 18.57 weeks (range 1.1 to 139.1 weeks) among the 67 patients in the 1/20 regimen.

The median duration of exposure of odronextamab was 14.86 weeks (range 0.9 to 76.0 weeks) among the 74 patients in the 0.7/4/20 regimen.

The reported difference in median duration of exposure was expected since that the patients treated in the 1/20 regimen had participated in the study longer at the time of the data cut.

Numbers analysed

Table 20 Number of patients included in each analysis population.

Analysis Set, n (%)	FL Grade 1-3a 80 mg (N=140)	MZL 80 mg (N=19)	MCL 160 mg (N=14)	Other B-NHL 160 mg (N=28)	DLBCL 160 mg (N=141)	DLBCL 320 mg (N=33)	Total (N=375)
Full Analysis Set	140 (100%)	19 (100%)	14 (100%)	28 (100%)	141 (100%)	33 (100%)	375 (100%)
Efficacy Analysis Set	128 (91.4%)	n/a	n/a	n/a	127 (90.0%)	33 (100%)	n/a[a]
Safety Analysis Set	140 (100%)	19 (100%)	14 (100%)	28 (100%)	141 (100%)	33 (100%)	375 (100%)
Pharmacokinetic Analysis Set	126 (90.0%)	19 (100%)	14 (100%)	28 (100%)	120 (85.1%)	33 (100%)	340 (90.7%)
Anti-drug Antibody Analysis Set	59 (42.1%)	17 (89.5%)	9 (64.3%)	12 (42.9%)	54 (38.3%)	22 (66.7%)	173 (46.1%)
Neutralizing Antibody Analysis Set	59 (42.1%)	17 (89.5%)	9 (64.3%)	12 (42.9%)	54 (38.3%)	22 (66.7%)	173 (46.1%)

[a] For this interim report, only FL grade 1-3a, DLBCL 160 mg, and DLBCL 320 mg cohorts were evaluated for efficacy (Section 5.1).
B-NHL, B-cell non-Hodgkin lymphoma; DLBCL, Diffuse large B-cell lymphoma; FL, Follicular lymphoma; MCL, Mantle cell lymphoma; MZL, Marginal zone lymphoma.

Full analysis set (FAS) included all enrolled patients who received any dose of odronextamab.

Efficacy Analysis Set included all enrolled patients who received any dose of odronextamab and had the opportunity for efficacy assessment at 12 weeks. A patient who started study treatment <77 days prior to data cutoff is not considered as having an opportunity for efficacy assessment at 12 weeks.

The FAS (n=281) in study 1625 included both the global cohort (n=255) and the Japan and China country-specific extension cohorts (n=26). The purpose of the country specific cohorts (Study 1625 Global Protocol Amendment 5) was to fulfill regulatory requirements in Japan and China, but they were not included in the primary efficacy analysis.

The primary efficacy analysis was limited to the global cohort where 128 FL 80 mg patients and 127 DLBCL 160 mg patients had the opportunity to have the 12-week assessment (Efficacy analysis set, which is also the FAS of the global cohort). Thus, the efficacy analyses in SmPC section 5.1 are based on the FAS from the global cohort.

- **Outcomes and estimation**

Table 21 Selected tumour characteristics FLGrade 1-3a by DCO 31 Jan 2023

	FL Grade 1-3a 1/20/80 mg (N=68)	FL Grade 1-3a 0.7/4/20/80 mg (N=60)	Total (N=128)
Ann Arbor Stage at Study Entry, n(%)			
I-II	10 (14.7%)	9 (15.0%)	19 (14.8%)
III-IV	58 (85.3%)	51 (85.0%)	109 (85.2%)
Bulky Disease, n(%)			
Yes	10 (14.7%)	8 (13.3%)	18 (14.1%)
No	58 (85.3%)	52 (86.7%)	110 (85.9%)
Refractory/Relapse at Study Entry, n(%)			
Refractory	51 (75.0%)	41 (68.3%)	92 (71.9%)
Relapse	17 (25.0%)	18 (30.0%)	35 (27.3%)
Unknown	0	1 (1.7%)	1 (0.8%)
Number of prior lines, median (range)			
Median	3.0	2.0	3.0
Min : Max	2 : 8	2 : 13	2 : 13
Risk Factors for FLIPI 1 in FL grade 1-3a, n(%)			
Low (0-1)	11 (16.2%)	10 (16.7%)	21 (16.4%)
Intermediate (2)	18 (26.5%)	15 (25.0%)	33 (25.8%)
High (3-5)	39 (57.4%)	35 (58.3%)	74 (57.8%)
FL POD24 Status, n(%)			
Yes	35 (51.5%)	28 (46.7%)	63 (49.2%)
No	33 (48.5%)	32 (53.3%)	65 (50.8%)

CD, Cluster of differentiation; FAS, Full analysis set; FL, Follicular lymphoma; FLIPI, Follicular Lymphoma International Prognostic Index; ICD-O, International Classification of Diseases for Oncology; NA, not applicable; POD24, Progress of Disease within 2 years of diagnosis

Note: Refractory at the study entry is defined as disease that progressed during previous therapy or relapsed within 6 months from completion of last line of therapy. Relapse at the study entry is defined as disease that recurred following a response lasting >6 months from completion of last line of therapy; also includes those with unknown/NA best response who, however, progressed/recurred >6 months from completion of last line of therapy.

Source: Module 5.3.5.2 R1979-ONC-1625 Interim CSR PTT 14.1.2.2.ea, 14.1.2.2.eo, 14.1.2.2.er, PTT 14.1.3.1.ea, 14.1.3.1.eo, 14.1.3.1.er.

The baseline data reflect a r/r FL population after multiple systemic therapies (at least 2), which is in line with the sought indication.

Prior lymphoma-related treatment

Of the 128 patients in the EAS with FL, 59 (46.1%) patients were refractory to first line and 92 (71.9%) were refractory to last line of treatment.

Ninety-five (74.2%) patients were refractory to prior anti-CD20 antibody, and 54 (42.2%) were double refractory to anti-CD20 antibody and alkylating agent.

Among 140 patients in the FAS, a total of 17 (13.3%) patients had prior rituximab and lenalidomide treatment. Fourteen percent of patients had received a prior PI3K inhibitor.

A total of 39/128 (30.5%) patients in the EAS had prior autologous stem-cell transplant.

Exposure, by DCO 31 Jan 2023

The median duration of exposure of odronextamab was 46.07 weeks (range 2.0 to 157.0 weeks) among the 68 patients in the 1/20 regimen.

The median duration of exposure of odronextamab was 24.07 weeks (range 0.4 to 73.3 weeks) among the 72 patients in the 0.7/4/20 regimen.

The reported difference in median duration of exposure was expected since that the patients treated in the 1/20 regimen had participated in the study longer at the time of the data cut.

DLBCL

Table 22 Selected demographics and baseline characteristics DLBCL by DCO 31 Jan 2023 - 160 mg cohort by step-up regimen (Efficacy Analysis Set)

	DLBCL 1/20/160 mg (N=67)	DLBCL 0.7/4/20/160 mg (N=60)	Total (N=127)
Age (years)			
n	67	60	127
Mean (SD)	63.3 (12.01)	65.3 (13.57)	64.3 (12.76)
Median	65.0	68.5	67.0
Q1 : Q3	53.0 : 72.0	59.0 : 75.0	55.0 : 74.0
Min : Max	29 : 88	24 : 85	24 : 88
Age groups (years), n (%)			
<65	33 (49.3%)	21 (35.0%)	54 (42.5%)
≥ 65	34 (50.7%)	39 (65.0%)	73 (57.5%)
Sex, n (%)			
Male	39 (58.2%)	37 (61.7%)	76 (59.8%)
Female	28 (41.8%)	23 (38.3%)	51 (40.2%)
Race, n (%)			
WHITE	29 (43.3%)	32 (53.3%)	61 (48.0%)
ASIAN	31 (46.3%)	22 (36.7%)	53 (41.7%)
OTHER	0	0	0
UNKNOWN	0	0	0
NOT REPORTED	7 (10.4%)	6 (10.0%)	13 (10.2%)
ECOG performance status, n (%)			
0	25 (37.3%)	16 (26.7%)	41 (32.3%)
1	42 (62.7%)	44 (73.3%)	86 (67.7%)
2	0	0	0
Geographic Region, n (%)			
North America	4 (6.0%)	7 (11.7%)	11 (8.7%)
Europe	26 (38.8%)	26 (43.3%)	52 (40.9%)
Asia-Pacific	37 (55.2%)	27 (45.0%)	64 (50.4%)
Rest of World	0	11 (20.4%)	11 (20.4%)

Data cutoff: 31 Jan 2023

[a] "Not reported" is affected by local country regulations.

DLBCL, diffuse large B-cell lymphoma; ECOG, eastern cooperative oncology group; Max, maximum; Min, minimum; Q1, quartile 1; Q3, quartile 3; SD, standard deviation.

Source: Module 5.3.5.2 R1979-ONC-1625 PTTs 14.1.2.1.er,14.1.2.1.eo, and 14.1.2.1.ea

Table 23 Selected tumour characteristics DLBCL by DCO 31 Jan 2023 Efficacy Analysis Set

	DLBCL 1/20/160 mg (N=67)	DLBCL 0.7/4/20/160 mg (N=60)	Total (N=127)
Ann Arbor Stage at Study Entry, n(%)			
I-II	15 (22.4%)	8 (13.3%)	23 (18.1%)
III-IV	52 (77.6%)	51 (85.0%)	103 (81.1%)
Missing		1 (1.7%)	1 (0.8%)
Bulky Disease, n(%)			
Yes	13 (19.4%)	15 (25.0%)	28 (22.0%)
No	54 (80.6%)	45 (75.0%)	99 (78.0%)
Refractory/Relapse at Study Entry, n(%)			
Refractory	58 (86.6%)	52 (86.7%)	110 (86.6%)
Relapse	9 (13.4%)	8 (13.3%)	17 (13.4%)
Number of prior lines			
Median	3.0	2.0	2.0
Min : Max	2 : 7	2 : 8	2 : 8
DLBCL cell of origin, n(%)			
Germinal Center B-Cell-like DLBCL	26 (38.8%)	17 (28.3%)	43 (33.9%)
Activated B-Cell-like DLBCL / Non-GCB	25 (37.3%)	31 (51.7%)	56 (44.1%)
Unclassified DLBCL	4 (6.0%)	0	4 (3.1%)
Missing	12 (17.9%)	12 (20.0%)	24 (18.9%)
DLBCL Subtype, n(%)			
DLBCL, denovo	45 (67.2%)	51 (85.0%)	96 (75.6%)
DLBCL, transformed (Richter)	5 (7.5%)	2 (3.3%)	7 (5.5%)
DLBCL, transformed (non-Richter)	17 (25.4%)	7 (11.7%)	24 (18.9%)

The baseline data reflect a r/r DLBCL population after multiple systemic therapies (at least 2), which is in line with the sought indication.

All 96 patients with DLBCL de novo had DLBCL NOS.

Based on the updated data from 20 October 2023 DCO, the number of HGBL patients in DLBCL 160 mg cohort was 11 (8.7%); this is composite of DLBCL, double-hit 5 (3.8%) and DLBCL, triple-hit 6 (4.7%). MYC translocation was required to be considered either a double hit or triple hit lymphoma. It is noted that testing for double-hit and triple-hit lymphoma was not done in 61 (48%) of the DLBCL patients in study 1625.

Prior lymphoma-related treatment

Of the 127 enrolled patients in the DLBCL 160 mg cohort, 70 (55.1%) were refractory to first line and 110 (86.6%) were refractory to last line of treatment.

Ninety-nine (78.0%) of patients were refractory to prior anti-CD20 antibody, and 82 (64.6%) were double refractory to anti-CD20 antibody and alkylating agent.

Twenty-two (17.3%) of the DLBCL patients had received prior autologous stem cell transplant.

Exposure, by DCO 31 Jan 2023

The median duration of exposure of odronextamab was 18.57 weeks (range 1.1 to 139.1 weeks) among the 67 patients in the 1/20 regimen.

The median duration of exposure of odronextamab was 14.86 weeks (range 0.9 to 76.0 weeks) among the 74 patients in the 0.7/4/20 regimen.

The reported difference in median duration of exposure was expected since that the patients treated in the 1/20 regimen had participated in the study longer at the time of the data cut.

Numbers analysed

Table 24 Number of patients included in each analysis population - Full analysis set (FAS)

Analysis Set, n (%)	FL Grade 1-3a 80 mg (N=140)	MZL 80 mg (N=19)	MCL 160 mg (N=14)	Other B-NHL 160 mg (N=28)	DLBCL 160 mg (N=141)	DLBCL 320 mg (N=33)	Total (N=375)
Full Analysis Set	140 (100%)	19 (100%)	14 (100%)	28 (100%)	141 (100%)	33 (100%)	375 (100%)
Efficacy Analysis Set	128 (91.4%)	n/a	n/a	n/a	127 (90.0%)	33 (100%)	n/a[a]
Safety Analysis Set	140 (100%)	19 (100%)	14 (100%)	28 (100%)	141 (100%)	33 (100%)	375 (100%)
Pharmacokinetic Analysis Set	126 (90.0%)	19 (100%)	14 (100%)	28 (100%)	120 (85.1%)	33 (100%)	340 (90.7%)
Anti-drug Antibody Analysis Set	59 (42.1%)	17 (89.5%)	9 (64.3%)	12 (42.9%)	54 (38.3%)	22 (66.7%)	173 (46.1%)
Neutralizing Antibody Analysis Set	59 (42.1%)	17 (89.5%)	9 (64.3%)	12 (42.9%)	54 (38.3%)	22 (66.7%)	173 (46.1%)

[a] For this interim report, only FL grade 1-3a, DLBCL 160 mg, and DLBCL 320 mg cohorts were evaluated for efficacy (Section 5.1).
B-NHL, B-cell non-Hodgkin lymphoma; DLBCL, Diffuse large B-cell lymphoma; FL, Follicular lymphoma; MCL, Mantle cell lymphoma; MZL, Marginal zone lymphoma.

Full analysis set (FAS) included all enrolled patients who received any dose of odronextamab.

Efficacy Analysis Set included all enrolled patients who received any dose of odronextamab and had the opportunity for efficacy assessment at 12 weeks. A patient who started study treatment <77 days prior to data cutoff is not considered as having an opportunity for efficacy assessment at 12 weeks.

The FAS (n=281) in study 1625 included both the global cohort (n=255) and the Japan and China country-specific extension cohorts (n=26). The purpose of the country specific cohorts (Study 1625 Global Protocol Amendment 5) was to fulfill regulatory requirements in Japan and China, but they were not included in the primary efficacy analysis.

The primary efficacy analysis was limited to the global cohort where 128 FL 80 mg patients and 127 DLBCL 160 mg patients had the opportunity to have the 12-week assessment (Efficacy analysis set, which is also the FAS of the global cohort).

Outcomes and estimation

FL

Data are available from an updated DCO by 20 Oct 2023. The updated median duration of study follow-up was 20.1 months (95% CI 17.3 to 27.8 months) for the FL cohort (n=128).

The median estimated duration of follow-up was 15.9 months (95% CI 14.7-17.2) for the 0.7/4/20 regimen vs 34.2 months (95% CI 33.2-35.7) for the 1/20 regimen.

Primary endpoint

Table 25 Response rate by ICR FL by updated DCO 20 Oct 2023

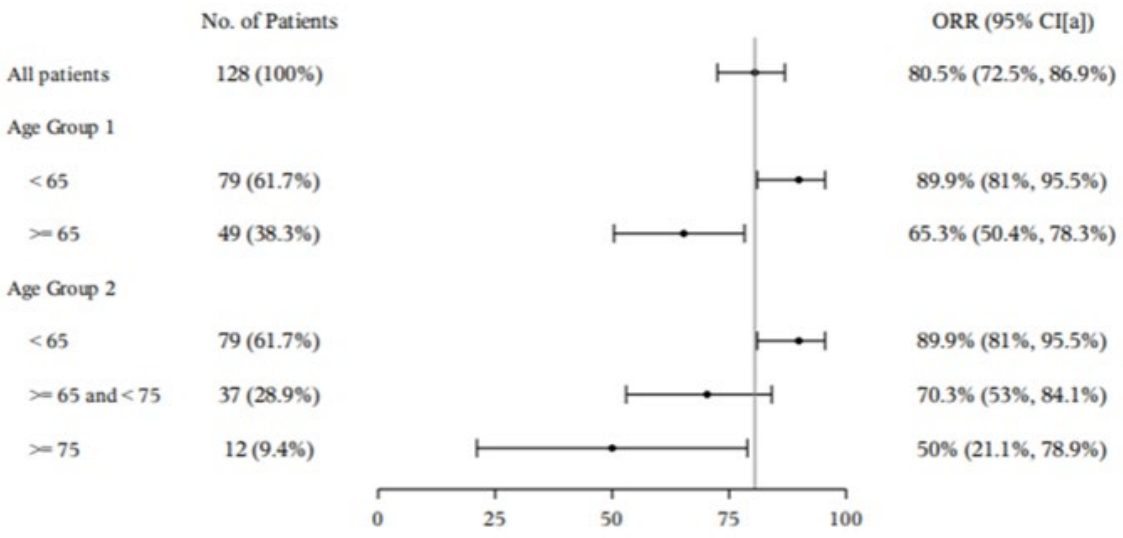
Table 14.2.1.1.ef Summary of Best Overall Response Rate based on Lugano Classification per Independent Central Reviewers
(Full Analysis Set)
FL Grade 1-3a Patients Who Had Opportunity for Response Assessment at 12 Weeks by Step-up Regimen

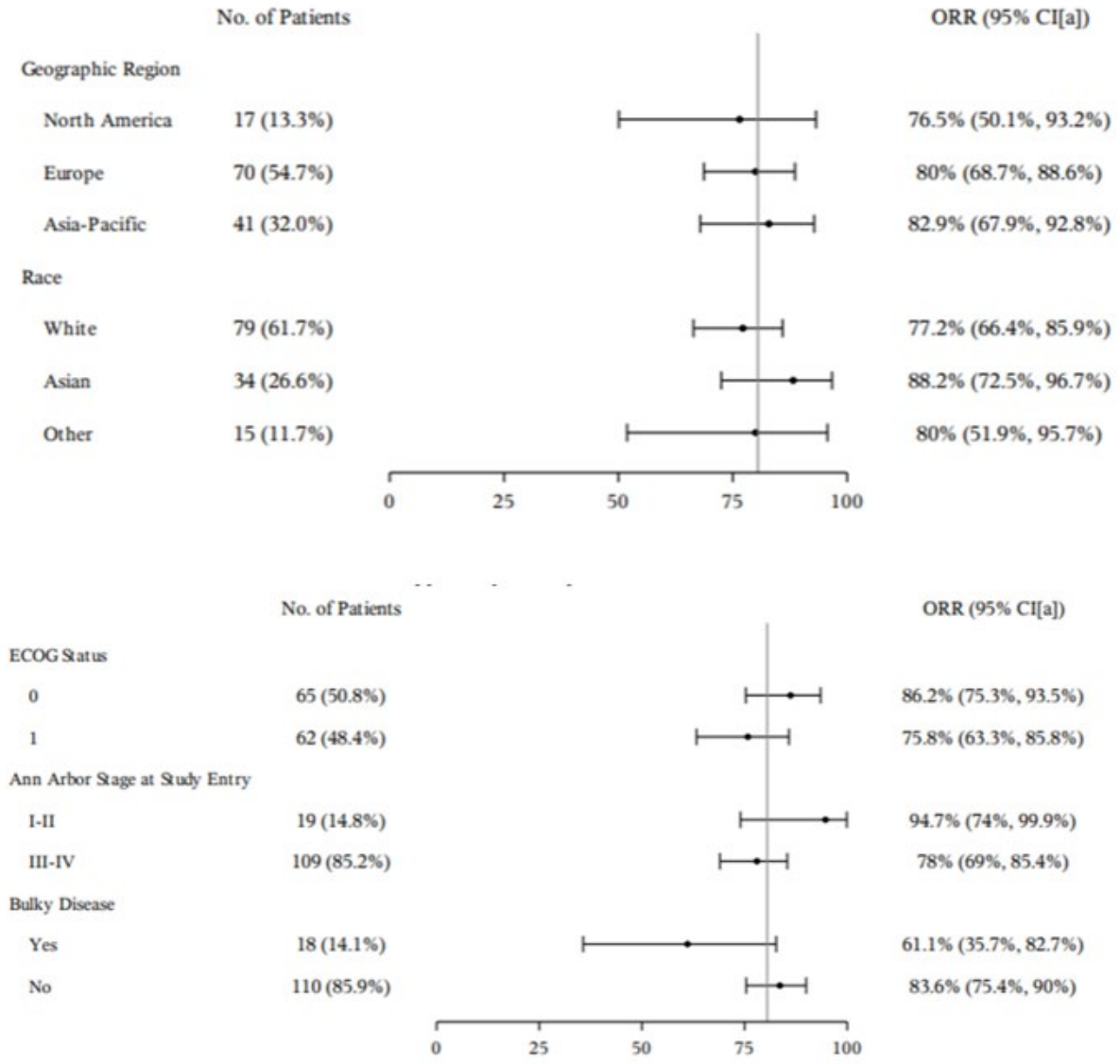
	FL Grade 1-3a 1/20/80 mg (N=68)	FL Grade 1-3a 0.7/4/20/80 mg (N=60)	Total (N=128)
Best Overall Tumor Response, n (%)			
Complete Response (CR)	52 (76.5%)	42 (70.0%)	94 (73.4%)
Partial Response (PR)	5 (7.4%)	4 (6.7%)	9 (7.0%)
Stable Disease (SD)	6 (8.8%)	3 (5.0%)	9 (7.0%)
Progressive Disease (PD)	1 (1.5%)	4 (6.7%)	5 (3.9%)
Not Evaluable (NE)	4 (5.9%)	7 (11.7%)	11 (8.6%)
Response			
Objective Response Rate (ORR:CR+PR)	57 (83.8%)	46 (76.7%)	103 (80.5%)
95% CI for ORR [a]	(72.9%, 91.6%)	(64.0%, 86.6%)	(72.5%, 86.9%)
95% CI for CR Rate [a]	(64.6%, 85.9%)	(56.8%, 81.2%)	(64.9%, 80.9%)
95% CI for PR Rate [a]	(2.4%, 16.3%)	(1.8%, 16.2%)	(3.3%, 12.9%)
Disease Control Rate (DCR: CR/PR/SD)	63 (92.6%)	49 (81.7%)	112 (87.5%)
95% CI for DCR [a]	(83.7%, 97.6%)	(69.6%, 90.5%)	(80.5%, 92.7%)

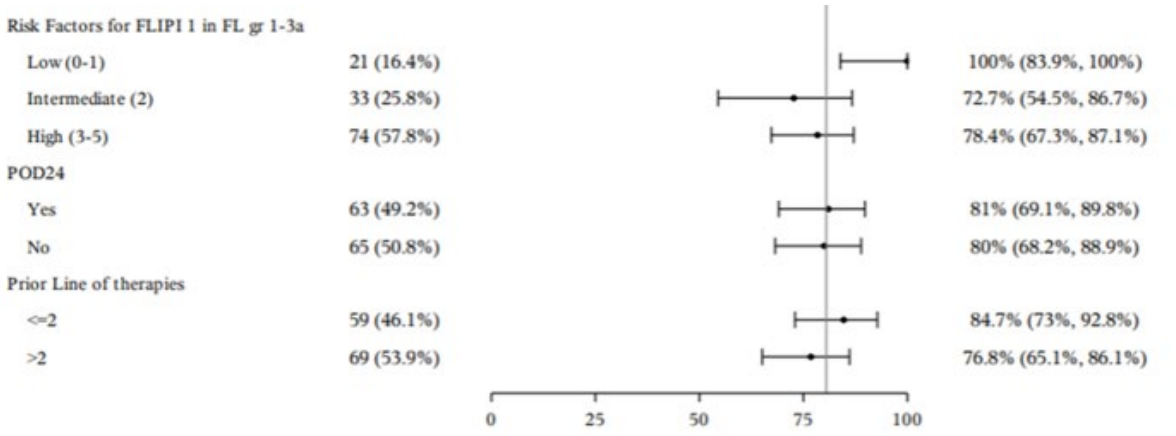
Data cut-off as of Oct 20th, 2023.
Patients who had opportunity for response assessment at 12 weeks exclude patients:
1) who started study drug <77 days prior to data cut off;
2) who started study drug >=77 days and <=91 days prior to cut off, and i) did not die, and ii) did not EOT (due to PD, loss to follow-up, withdrew consent) and EOS, and iii) did not have a tumor assessment within this window.
[a] Clopper-Person exact confidence interval.

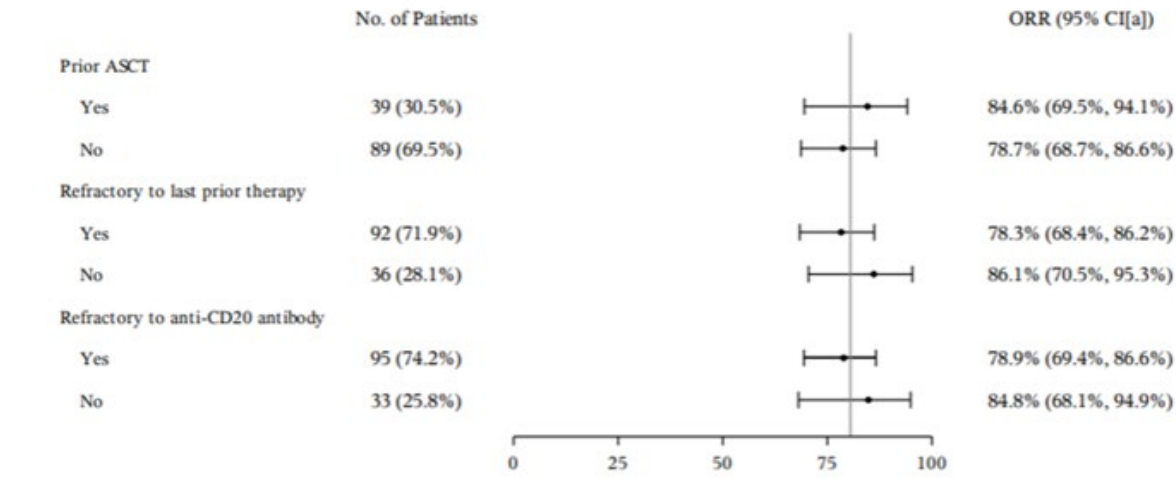
Subgroup analysis for ORR is presented in figure below by updated DCO 20 Oct 2023.

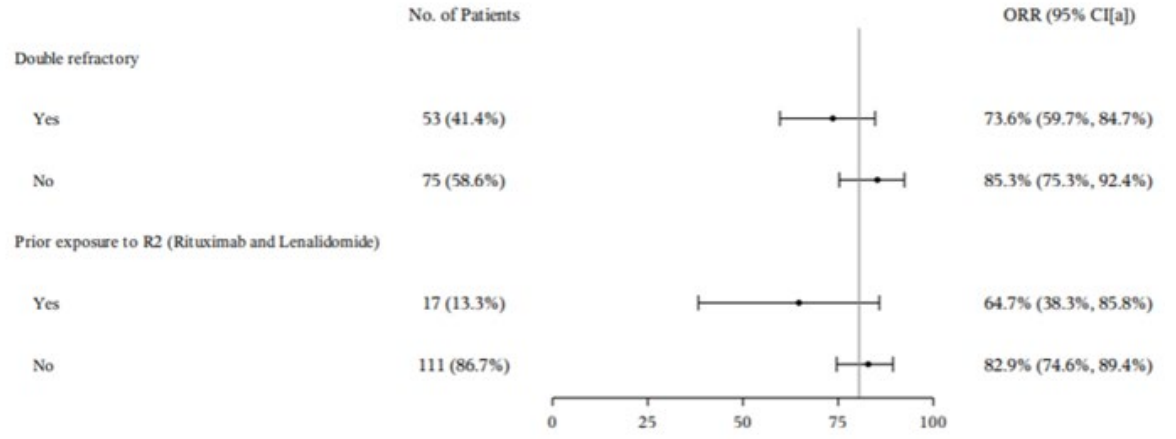
Figure 9 Forest plot for ORR by subgroup per IRC FL grade 1-3a by updated DCO 20 Oct 2023


No. of Patients
ORR (95% CI[a])
All patients
128 (100%)
80.5% (72.5%, 86.9%)
Age Group 1
< 65
79 (61.7%)
89.9% (81%, 95.5%)
>= 65
49 (38.3%)
65.3% (50.4%, 78.3%)
Age Group 2
< 65
79 (61.7%)
89.9% (81%, 95.5%)
>= 65 and < 75
37 (28.9%)
70.3% (53%, 84.1%)
>= 75
12 (9.4%)
50% (21.1%, 78.9%)
0
25
50
75
100


No. of Patients
ORR (95% CI[a])
Geographic Region
North America 17 (13.3%) 76.5% (50.1%, 93.2%)
Europe 70 (54.7%) 80% (68.7%, 88.6%)
Asia-Pacific 41 (32.0%) 82.9% (67.9%, 92.8%)
Race
White 79 (61.7%) 77.2% (66.4%, 85.9%)
Asian 34 (26.6%) 88.2% (72.5%, 96.7%)
Other 15 (11.7%) 80% (51.9%, 95.7%)
0 25 50 75 100
No. of Patients
ORR (95% CI[a])
ECOG Status
0 65 (50.8%) 86.2% (75.3%, 93.5%)
1 62 (48.4%) 75.8% (63.3%, 85.8%)
Ann Arbor Stage at Study Entry
I-II 19 (14.8%) 94.7% (74%, 99.9%)
III-IV 109 (85.2%) 78% (69%, 85.4%)
Bulky Disease
Yes 18 (14.1%) 61.1% (35.7%, 82.7%)
No 110 (85.9%) 83.6% (75.4%, 90%)
0 25 50 75 100







At the updated DCO 20 Oct 2023, ORR (primary endpoint, n=128) was 80.5% (95% CI: 72.5%, 86.9%), with a CR in 73.4% (95% CI: 64.9%, 80.9%) of the patients. This is considered to be clinically relevant in patients with r/r FL after 2 prior lines of therapy.

The lower bound of the 95% CI for ORR exceeded the 49% rate prespecified ORR in the SAP, which was chosen by the applicant as the minimum clinically meaningful ORR for the FL cohort.

Despite the single-arm study design and limited sample size, activity of odronextamab is evident and can be isolated. Spontaneous remissions are not expected in r/r FL after 2 prior lines in patients for whom systemic therapy is indicated.

Four patients in the 1/20 mg cohort were not evaluable for primary endpoint due to discontinuation of study treatment before the opportunity for first tumour assessment at week 12 because of adverse event (n=1), death (n=2), or withdrawal by subject (n=1). Seven patients in the 0.7/4/20 cohort were not evaluable for primary endpoint due to discontinuation of study treatment before the opportunity for first tumour assessment at week 12 because of withdrawal of consent (n=3), subject decision (n=1), physician decision (n=1), adverse advent (n=1), or death (n=1). These subjects are adequately considered as failures in the primary endpoint ORR analysis.

According to the subgroup analysis, the ORR results are not considered to be driven by a specific subgroup. However, numerically lower ORR rates are noted in older patients > 75 years and in patients with bulky disease, which may be expected.

Secondary endpoints

Table 26 Response rate by Investigator FL by DCO 20 Oct 2023

FL Grade 1-3a Patients Who Had Opportunity for Response Assessment at 12 Weeks by Step-up Regimen

	FL Grade 1-3a 1/20/80 mg (N=68)	FL Grade 1-3a 0.7/4/20/80 mg (N=60)	Total (N=128)
Best Overall Tumor Response, n (%)			
Complete Response (CR)	51 (75.0%)	42 (70.0%)	93 (72.7%)
Partial Response (PR)	5 (7.4%)	7 (11.7%)	12 (9.4%)
Stable Disease (SD)	3 (4.4%)	1 (1.7%)	4 (3.1%)
Progressive Disease (PD)	5 (7.4%)	3 (5.0%)	8 (6.3%)
Not Evaluable (NE)	4 (5.9%)	7 (11.7%)	11 (8.6%)
Response			
Objective Response Rate (ORR:CR+PR)	56 (82.4%)	49 (81.7%)	105 (82.0%)
95% CI for ORR [a]	(71.2%, 90.5%)	(69.6%, 90.5%)	(74.3%, 88.3%)
95% CI for CR Rate [a]	(63.0%, 84.7%)	(56.8%, 81.2%)	(64.1%, 80.2%)
95% CI for PR Rate [a]	(2.4%, 16.3%)	(4.8%, 22.6%)	(4.9%, 15.8%)
Disease Control Rate (DCR: CR/PR/SD)	59 (86.8%)	50 (83.3%)	109 (85.2%)
95% CI for DCR [a]	(76.4%, 93.8%)	(71.5%, 91.7%)	(77.8%, 90.8%)

Data cut-off as of Oct 20th, 2023.

CI, Confidence interval; CR, Complete response; DCR, Disease control rate;; FL, Follicular lymphoma; ORR, Objective response rate; PD, Progressive disease; PR, Partial response; NE, Not evaluable; SD, Stable disease..
Source: Module 5.3.5.2 R1979-ONC-1625 Interim CSR Table 14.

There was concordance in the **response rates noted by investigator assessment** and IRC.

Table 27 Duration of response and Duration of complete response per IRC by updated DCO 20 Oct 2023

Table 14.2.1.5.ef Kaplan-Meier Estimation of Duration of Response based on Lugano Classification per Independent Central Reviewers
(Full Analysis Set)
FL Grade 1-3a Patients with CR/PR Who Had Opportunity for Response Assessment at 12 Weeks by Step-up Regimen

	FL Grade 1-3a 1/20/80 mg (N=57)	FL Grade 1-3a 0.7/4/20/80 mg (N=46)	Total (N=103)
KM Estimation of Duration of Response (CR or PR) (months) [a]			
n	57	46	103
Number of events, n (%)	33 (57.9%)	10 (21.7%)	43 (41.7%)
Progressive Disease per Lugano, n (%)	22 (38.6%)	7 (15.2%)	29 (28.2%)
Death, n (%)	11 (19.3%)	3 (6.5%)	14 (13.6%)
Number of censored patients, n (%)	24 (42.1%)	36 (78.3%)	60 (58.3%)
Median (95% CI), (months)	20.5 (14.8, 32.2)	NR (17.0, NE)	22.6 (17.7, NE)

Data cut-off as of Oct 20th, 2023.
Patients who had opportunity for response assessment at 12 weeks exclude patients:
1) who started study drug <77 days prior to data cut off;
2) who started study drug >=77 days and <=91 days prior to cut off, and i) did not die, and ii) did not EOT (due to PD, loss to follow-up, withdrew consent) and EOS, and iii) did not have a tumor assessment within this window.
[a] Based on patients with CR or PR.

Table 14.2.1.5.ef Kaplan-Meier Estimation of Duration of Response based on Lugano Classification per Independent Central Reviewers
(Full Analysis Set)
FL Grade 1-3a Patients with CR/PR Who Had Opportunity for Response Assessment at 12 Weeks by Step-up Regimen

	FL Grade 1-3a 1/20/80 mg (N=57)	FL Grade 1-3a 0.7/4/20/80 mg (N=46)	Total (N=103)
Estimated Event-Free Probability , % (95% CI)[a]			
3 months	83.5 (70.7, 91.0)	93.2 (80.5, 97.8)	87.9 (79.7, 92.9)
6 months	74.2 (60.4, 83.8)	88.3 (74.2, 95.0)	80.5 (71.2, 87.1)
9 months	70.5 (56.4, 80.7)	85.9 (71.2, 93.4)	77.3 (67.6, 84.4)
12 months	66.6 (52.4, 77.5)	78.4 (62.5, 88.1)	71.8 (61.6, 79.8)
15 months	62.7 (48.3, 74.1)	78.4 (62.5, 88.1)	68.9 (58.3, 77.4)
18 months	54.4 (39.9, 66.7)	69.7 (45.5, 84.7)	59.9 (47.9, 70.0)
21 months	48.1 (33.9, 60.9)	NE (NE, NE)	53.3 (40.5, 64.5)
24 months	41.8 (28.1, 54.9)	NE (NE, NE)	46.3 (33.2, 58.5)
27 months	37.6 (24.4, 50.8)	NE (NE, NE)	41.7 (28.6, 54.3)
30 months	37.6 (24.4, 50.8)	NE (NE, NE)	41.7 (28.6, 54.3)
33 months	34.2 (21.0, 47.9)	NE (NE, NE)	37.9 (24.3, 51.4)
36 months	34.2 (21.0, 47.9)	NE (NE, NE)	37.9 (24.3, 51.4)
39 months	34.2 (21.0, 47.9)	NE (NE, NE)	37.9 (24.3, 51.4)
42 months	34.2 (21.0, 47.9)	NE (NE, NE)	37.9 (24.3, 51.4)
45 months	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)

Data cut-off as of Oct 20th, 2023.
Patients who had opportunity for response assessment at 12 weeks exclude patients:
1) who started study drug <77 days prior to data cut off;
2) who started study drug >=77 days and <=91 days prior to cut off, and i) did not die, and ii) did not EOT (due to PD, loss to follow-up, withdrew consent) and EOS, and iii) did not have a tumor assessment within this window.
[a] Based on patients with CR or PR.

Table 14.2.1.15.ef Kaplan-Meier Estimation of Duration of Complete Response based on Lugano Classification per Independent Central Reviewers
(Full Analysis Set)
FL Grade 1-3a Patients with CR Who Had Opportunity for Response Assessment at 12 Weeks by Step-up Regimen

	FL Grade 1-3a 1/20/80 mg (N=52)	FL Grade 1-3a 0.7/4/20/80 mg (N=42)	Total (N=94)
KM Estimation of Duration of Complete Response (CR) (months) [a]			
n	52	42	94
Number of events, n (%)	29 (55.8%)	7 (16.7%)	36 (38.3%)
Progressive Disease per Lugano, n (%)	19 (36.5%)	6 (14.3%)	25 (26.6%)
Death, n (%)	10 (19.2%)	1 (2.4%)	11 (11.7%)
Number of censored patients, n (%)	23 (44.2%)	35 (83.3%)	58 (61.7%)
Median (95% CI), (months)	20.8 (16.4, NE)	NR (NE, NE)	25.1 (20.5, NE)

Data cut-off as of Oct 20th, 2023.
Patients who had opportunity for response assessment at 12 weeks exclude patients:
1) who started study drug <77 days prior to data cut off;
2) who started study drug >=77 days and <=91 days prior to cut off, and i) did not die, and ii) did not EOT (due to PD, loss to follow-up, withdrew consent) and EOS, and iii) did not have a tumor assessment within this window.
[a] Based on patients with CR.

Table 14.2.1.15.ef Kaplan-Meier Estimation of Duration of Complete Response based on Lugano Classification per Independent Central Reviewers
(Full Analysis Set)
FL Grade 1-3a Patients with CR Who Had Opportunity for Response Assessment at 12 Weeks by Step-up Regimen

	FL Grade 1-3a 1/20/80 mg (N=52)	FL Grade 1-3a 0.7/4/20/80 mg (N=42)	Total (N=94)
Estimated Event-Free Probability , % (95% CI)[a]			
3 months	86.1 (73.0, 93.1)	95.1 (81.7, 98.7)	90.1 (81.9, 94.7)
6 months	76.1 (61.8, 85.7)	89.6 (74.6, 96.0)	82.1 (72.4, 88.6)
9 months	74.1 (59.6, 84.1)	86.9 (71.3, 94.3)	79.8 (69.8, 86.8)
12 months	70.0 (55.2, 80.7)	81.3 (64.6, 90.6)	74.9 (64.4, 82.7)
15 months	67.9 (53.0, 78.9)	81.3 (64.6, 90.6)	73.4 (62.7, 81.5)
18 months	58.8 (43.6, 71.2)	81.3 (64.6, 90.6)	65.3 (52.8, 75.2)
21 months	49.8 (34.8, 63.0)	NE (NE, NE)	55.4 (41.4, 67.3)
24 months	45.2 (30.6, 58.8)	NE (NE, NE)	50.4 (36.1, 63.0)
27 months	40.6 (26.4, 54.3)	NE (NE, NE)	45.2 (30.9, 58.4)
30 months	40.6 (26.4, 54.3)	NE (NE, NE)	45.2 (30.9, 58.4)
33 months	36.9 (22.6, 51.2)	NE (NE, NE)	41.1 (26.3, 55.3)
36 months	36.9 (22.6, 51.2)	NE (NE, NE)	41.1 (26.3, 55.3)
39 months	36.9 (22.6, 51.2)	NE (NE, NE)	41.1 (26.3, 55.3)
42 months	36.9 (22.6, 51.2)	NE (NE, NE)	41.1 (26.3, 55.3)
45 months	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)

Data cut-off as of Oct 20th, 2023.
Patients who had opportunity for response assessment at 12 weeks exclude patients:
1) who started study drug <77 days prior to data cut off;
2) who started study drug >=77 days and <=91 days prior to cut off, and i) did not die, and ii) did not EOT (due to PD, loss to follow-up, withdrew consent) and EOS, and iii) did not have a tumor assessment within this window.
[a] Based on patients with CR.

Among the 45 FL patients who were eligible (i.e., remained on treatment for at least 9 months of CR) and transitioned from Q2W to Q4W dosing; 9 patients had progressive disease as of the updated data cutoff 20 Oct 2023. The estimated median duration of response from time of transition in was 22.8 months (95% CI: 11.2, NE). Seven of the 45 FL patients that transitioned to Q4W had low or negative CD20 score of which 1 patient progressed after transition. Seventeen patients had CD20 expression H-score > 50 and none of these patients progressed after transition. Twenty one patients had unknown CD20 status of which 8 patients progressed after transition.

Table 28 Time to response and Time to Complete response per IRC by updated DCO 20 Oct 2023

Table 14.2.1.29.ef Observed Time to Response based on Lugano Classification per Independent Central Reviewers
(Full Analysis Set)
FL Grade 1-3a Patients with CR/PR Who Had Opportunity for Response Assessment at 12 Weeks by Step-up Regimen

	FL Grade 1-3a 1/20/80 mg (N=57)	FL Grade 1-3a 0.7/4/20/80 mg (N=46)	Total (N=103)
Observed Time to Response (CR or PR) (months) [a]			
n	57	46	103
Mean (SD)	2.73 (0.438)	2.85 (0.881)	2.79 (0.672)
Median	2.60	2.66	2.66
Q1 : Q3	2.46 : 2.79	2.56 : 2.79	2.53 : 2.79
Min : Max	2.4 : 4.4	1.8 : 7.9	1.8 : 7.9
Observed Time to Response (CR or PR), n (%) [a]			
<6 weeks	0	0	0
>=6 weeks and <3 months	49 (86.0%)	42 (91.3%)	91 (88.3%)
>=3 months and <6 months	8 (14.0%)	3 (6.5%)	11 (10.7%)
>=6 months and <9 months	0	1 (2.2%)	1 (1.0%)
>=9 months	0	0	0

Data cut-off as of Oct 20th, 2023
Patients who had opportunity for response assessment at 12 weeks exclude patients:
1) who started study drug <77 days prior to data cut off,
2) who started study drug >=77 days and <=91 days prior to cut off, and i) did not die, and ii) did not EOT (due to PD, loss to follow-up, withdrew consent) and EOS, and iii) did not have a tumor assessment within this window.
[a] Based on patients with CR or PR.

Table 14.2.1.33.ef Observed Time to Complete Response based on Lugano Classification per Independent Central Reviewers
(Full Analysis Set)
FL Grade 1-3a Patients with CR Who Had Opportunity for Response Assessment at 12 Weeks by Step-up Regimen

	FL Grade 1-3a 1/20/80 mg (N=52)	FL Grade 1-3a 0.7/4/20/80 mg (N=42)	Total (N=94)
Observed Time to Complete Response (CR) (months) [a]			
n	52	42	94
Mean (SD)	2.85 (0.679)	2.93 (0.945)	2.88 (0.805)
Median	2.64	2.68	2.66
Q1 : Q3	2.48 : 2.87	2.56 : 2.79	2.53 : 2.83
Min : Max	2.4 : 6.3	2.3 : 7.9	2.3 : 7.9
Observed Time to Complete Response (CR), n (%) [a]			
<6 weeks	0	0	0
>=6 weeks and <3 months	42 (80.8%)	38 (90.5%)	80 (85.1%)
>=3 months and <6 months	9 (17.3%)	3 (7.1%)	12 (12.8%)
>=6 months and <9 months	1 (1.9%)	1 (2.4%)	2 (2.1%)
>=9 months	0	0	0

Data cut-off as of Oct 20th, 2023.
Patients who had opportunity for response assessment at 12 weeks exclude patients:
1) who started study drug <77 days prior to data cut off,
2) who started study drug >=77 days and <=91 days prior to cut off, and i) did not die, and ii) did not EOT (due to PD, loss to follow-up, withdrew consent) and EOS, and iii) did not have a tumor assessment within this window.
[a] Based on patients with CR.

The first response assessment per protocol was at week 12, therefore quantification of **Time to response/Time to complete response** before that time was not possible.

Time to response and Time to complete response were similar between the two different step-up regimens. However, most responses (88.3%) were evident by the time of first response assessment at week 12. The median observed TTR was 2.7 months (range: 1.8 to 7.9). Further, most CRs (85.1%) patients) were evident by the time of first response assessment, and median observed TTCR was 2.7 months (range 2.3 to 7.9).

Secondary endpoint **PFS**

Table 29 PFS per IRC by DCO 20 Oct 2023

Table 14.2.3.1.ef Progression-free Survival per Independent Central Reviewers
(Full Analysis Set)
FL Grade 1-3a Patients Who Had Opportunity for Response Assessment at 12 Weeks with 1/20 mg Step-up Regimen

	FL Grade 1-3a 1/20/80 mg (N=68)	FL Grade 1-3a 0.7/4/20/80 mg (N=60)	Total (N=128)
Number of events, n (%)	42 (61.8%)	20 (33.3%)	62 (48.4%)
Progressive Disease per Lugano, n (%)	26 (38.2%)	13 (21.7%)	39 (30.5%)
Death, n (%)	16 (23.5%)	7 (11.7%)	23 (18.0%)
Number of censored patients, n (%)	26 (38.2%)	40 (66.7%)	66 (51.6%)
Median (95% CI), (months)	20.2 (12.5, 26.5)	NR (19.5, NE)	20.7 (17.2, 27.5)

Data cut-off as of Oct 20th, 2023.
Patients who had opportunity for response assessment at 12 weeks exclude patients:
1) who started study drug <77 days prior to data cut off;
2) who started study drug >=77 days and <=91 days prior to cut off, and i) did not die, and ii) did not EOT (due to PD, loss to follow-up, withdrew consent) and EOS, and iii) did not have a tumor assessment within this window.
[a] Based on Kaplan-Meier method.

Table 14.2.3.1.ef Progression-free Survival per Independent Central Reviewers
(Full Analysis Set)
FL Grade 1-3a Patients Who Had Opportunity for Response Assessment at 12 Weeks with 1/20 mg Step-up Regimen

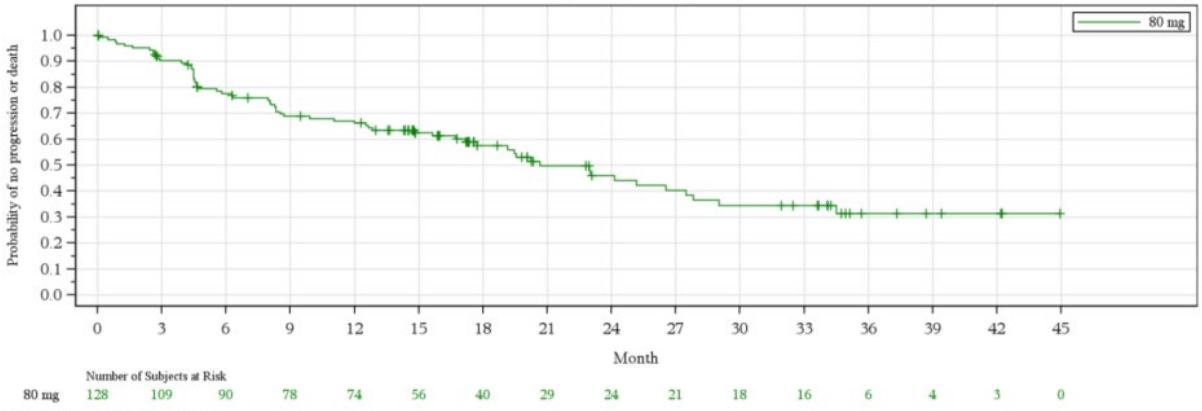
	FL Grade 1-3a 1/20/80 mg (N=68)	FL Grade 1-3a 0.7/4/20/80 mg (N=60)	Total (N=128)
Estimated Event-Free Probability , % (95% CI)[a]			
3 months	92.5 (82.9, 96.8)	87.5 (75.6, 93.8)	90.3 (83.5, 94.4)
6 months	76.8 (64.5, 85.3)	78.4 (65.1, 87.1)	77.7 (69.1, 84.1)
9 months	65.6 (52.6, 75.9)	72.5 (58.6, 82.5)	68.9 (59.7, 76.4)
12 months	64.0 (50.9, 74.4)	68.6 (54.4, 79.2)	66.2 (56.9, 74.0)
15 months	60.7 (47.5, 71.5)	64.6 (50.1, 75.8)	62.4 (52.9, 70.5)
18 months	53.9 (40.7, 65.3)	64.6 (50.1, 75.8)	57.5 (47.6, 66.2)
21 months	46.7 (33.8, 58.6)	57.4 (38.2, 72.6)	49.7 (39.1, 59.5)
24 months	43.1 (30.4, 55.1)	NE (NE, NE)	46.1 (35.1, 56.3)
27 months	37.7 (25.5, 49.8)	NE (NE, NE)	40.3 (29.1, 51.2)
30 months	32.3 (20.8, 44.4)	NE (NE, NE)	34.5 (23.5, 45.8)
33 months	32.3 (20.8, 44.4)	NE (NE, NE)	34.5 (23.5, 45.8)
36 months	29.4 (17.9, 41.8)	NE (NE, NE)	31.4 (20.1, 43.3)
39 months	29.4 (17.9, 41.8)	NE (NE, NE)	31.4 (20.1, 43.3)
42 months	29.4 (17.9, 41.8)	NE (NE, NE)	31.4 (20.1, 43.3)
45 months	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)

Data cut-off as of Oct 20th, 2023.
Patients who had opportunity for response assessment at 12 weeks exclude patients:
1) who started study drug <77 days prior to data cut off;
2) who started study drug >=77 days and <=91 days prior to cut off, and i) did not die, and ii) did not EOT (due to PD, loss to follow-up, withdrew consent) and EOS, and iii) did not have a tumor assessment within this window.
[a] Based on Kaplan-Meier method.

Figure 10 PFS per IRC by DCO 20 Oct 2023

Protocol: R1979-ONC-1625

Figure 14.2.3.1.efa Kaplan-Meier Curve of Progression-free Survival per Independent Central Reviewers
(Full Analysis Set)
FL Grade 1-3a Patients Who Had Opportunity for Response Assessment at 12 Weeks



Number of Subjects at Risk															
80 mg	128	109	90	78	74	56	40	29	24	21	18	16	6	4	3	0

Data cut-off as of Oct 20th, 2023.
Patients who had opportunity for response assessment at 12 weeks exclude patients:
1) who started study drug <77 days prior to data cut off;
2) who started study drug >=77 days and <=91 days prior to cut off, and i) did not die, and ii) did not EOT (due to PD, loss to follow-up, withdrew consent) and EOS, and iii) did not have a tumor assessment within this window.

By updated DCO 20 Oct 2023, the median PFS was 20.7 months (95% CI 17.2 to 27.5).

Secondary endpoint OS

Table 30 OS by DCO 20 Oct 2023

Table 14.2.2.1.ef Overall Survival
(Full Analysis Set)
FL Grade 1-3a Patients Who Had Opportunity for Response Assessment at 12 Weeks by Step-up Regimen

	FL Grade 1-3a 1/20/80 mg (N=68)	FL Grade 1-3a 0.7/4/20/80 mg (N=60)	Total (N=128)
Number of deaths, n (%)	27 (39.7%)	10 (16.7%)	37 (28.9%)
Number of censored patients, n (%)	41 (60.3%)	50 (83.3%)	91 (71.1%)
Median (95% CI), (months)[a]	NR (27.5, NE)	NR (NE, NE)	NR (32.4, NE)

Data cut-off as of Oct 20th, 2023.
Patients who had opportunity for response assessment at 12 weeks exclude patients:
1) who started study drug <77 days prior to data cut off,
2) who started study drug >=77 days and <=91 days prior to cut off, and i) did not die, and ii) did not EOT (due to PD, loss to follow-up, withdrew consent) and EOS, and iii) did not have a tumor assessment within this window.
[a] Based on Kaplan-Meier method.

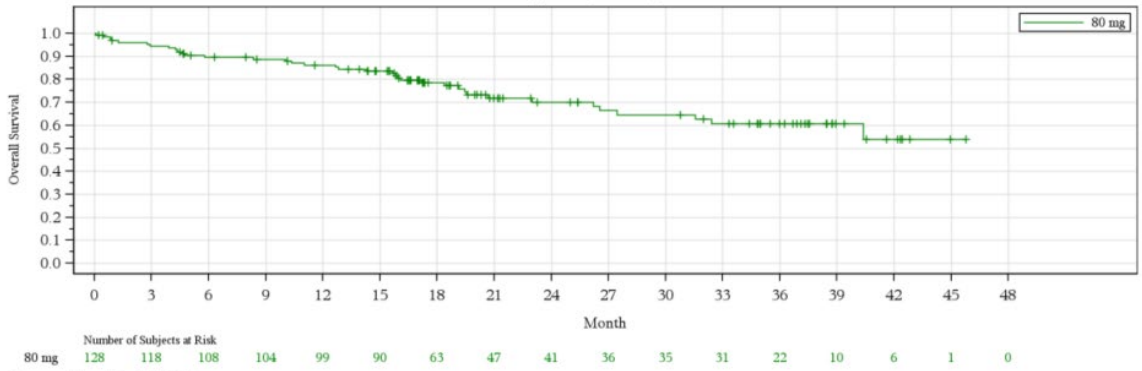
Table 14.2.2.1.ef Overall Survival
(Full Analysis Set)
FL Grade 1-3a Patients Who Had Opportunity for Response Assessment at 12 Weeks by Step-up Regimen

	FL Grade 1-3a 1/20/80 mg (N=68)	FL Grade 1-3a 0.7/4/20/80 mg (N=60)	Total (N=128)
Estimated Survival Probability , % (95% CI)[a]			
3 months	94.1 (85.1, 97.8)	94.9 (85.0, 98.3)	94.4 (88.7, 97.3)
6 months	89.7 (79.6, 94.9)	89.5 (78.1, 95.1)	89.6 (82.7, 93.8)
9 months	88.2 (77.7, 93.9)	89.5 (78.1, 95.1)	88.7 (81.7, 93.2)
12 months	85.1 (74.1, 91.7)	87.5 (75.5, 93.9)	86.2 (78.7, 91.2)
15 months	82.1 (70.6, 89.4)	85.5 (73.0, 92.5)	83.5 (75.6, 89.1)
18 months	75.7 (63.4, 84.4)	83.0 (69.6, 90.8)	78.5 (69.7, 85.0)
21 months	69.1 (56.3, 78.9)	76.6 (56.9, 88.2)	71.8 (61.7, 79.6)
24 months	67.5 (54.5, 77.5)	76.6 (56.9, 88.2)	70.1 (59.7, 78.3)
27 months	63.9 (50.7, 74.4)	NE (NE, NE)	66.4 (55.2, 75.4)
30 months	62.1 (48.9, 72.9)	NE (NE, NE)	64.6 (53.1, 73.9)
33 months	58.4 (45.0, 69.6)	NE (NE, NE)	60.7 (48.7, 70.8)
36 months	58.4 (45.0, 69.6)	NE (NE, NE)	60.7 (48.7, 70.8)
39 months	58.4 (45.0, 69.6)	NE (NE, NE)	60.7 (48.7, 70.8)
42 months	51.9 (34.7, 66.6)	NE (NE, NE)	54.0 (37.0, 68.2)
45 months	51.9 (34.7, 66.6)	NE (NE, NE)	54.0 (37.0, 68.2)
48 months	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)

Data cut-off as of Oct 20th, 2023.
Patients who had opportunity for response assessment at 12 weeks exclude patients:
1) who started study drug <77 days prior to data cut off,
2) who started study drug >=77 days and <=91 days prior to cut off, and i) did not die, and ii) did not EOT (due to PD, loss to follow-up, withdrew consent) and EOS, and iii) did not have a tumor assessment within this window.
[a] Based on Kaplan-Meier method.

Figure 11 OS by DCO 20 Oct 2023

Figure 14.2.2.1.efa Kaplan-Meier Curve of Overall Survival
(Full Analysis Set)
FL Grade 1-3a Patients Who Had Opportunity for Response Assessment at 12 Weeks



Data cut-off as of Oct 20th, 2023.
Patients who had opportunity for response assessment at 12 weeks exclude patients:
1) who started study drug <77 days prior to data cut off;
2) who started study drug >=77 days and <=91 days prior to cut off, and i) did not die, and ii) did not EOT (due to PD, loss to follow-up, withdrew consent) and EOS, and iii) did not have a tumor assessment within this window.

By updated DCO 20 Oct 2023, the median OS was NE (95% CI 32.4 to NE).

PFS and OS (secondary endpoints) are time dependent endpoints that do not isolate drug effects in a single-arm trial.

As no **PRO**-based claims are suggested in the SmPC, no thorough assessment was performed of the PRO methodology or results.

DLBCL

Follow-up data from an updated DCO 20 Oct 2023 are available. The updated median duration of study follow-up was 32.5 months (95% CI 17.4 to 36.3 months) for the DLBCL cohort (n=127).

The median estimated duration of follow-up was 17.3 months (95% CI 12.4-23.0) for the 0.7/4/20 mg regimen vs 36.3 months (95% CI 32.5-38.8) for the 1/20 mg regimen.

Primary endpoint

Table 31 Response rate per IRC DLBCL by updated DCO 20 Oct 2023

Table 14.2.1.1.ed Summary of Best Overall Response Rate based on Lugano Classification per Independent Central Reviewers
(Full Analysis Set)
DLBCL Patients Who Had Opportunity for Response Assessment at 12 Weeks by Step-up Regimen and Dose

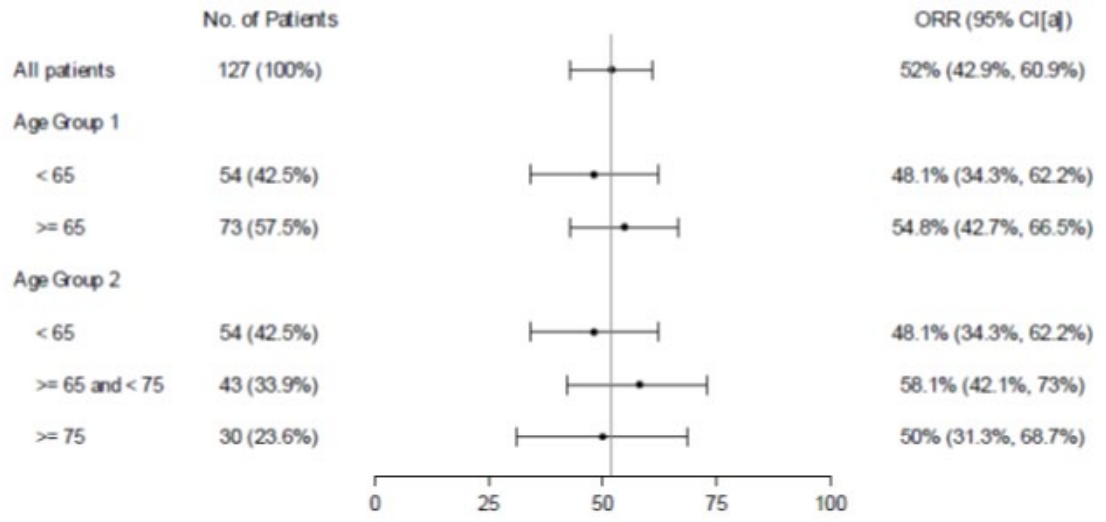
	DLBCL 1/20/160 mg (N=67)	DLBCL 0.7/4/20/160 mg (N=60)	Subtotal for DLBCL 160 mg (N=127)	DLBCL 1/20/320 mg (N=33)
Best Overall Tumor Response, n (%)				
Complete Response (CR)	23 (34.3%)	17 (28.3%)	40 (31.5%)	13 (39.4%)
Partial Response (PR)	12 (17.9%)	14 (23.3%)	26 (20.5%)	6 (18.2%)
Stable Disease (SD)	5 (7.5%)	5 (8.3%)	10 (7.9%)	2 (6.1%)
Progressive Disease (PD)	13 (19.4%)	10 (16.7%)	23 (18.1%)	6 (18.2%)
Not Evaluable (NE)	14 (20.9%)	14 (23.3%)	28 (22.0%)	6 (18.2%)
Response				
Objective Response Rate (ORR:CR+PR)	35 (52.2%)	31 (51.7%)	66 (52.0%)	19 (57.6%)
95% CI for ORR [a]	(39.7%, 64.6%)	(38.4%, 64.8%)	(42.9%, 60.9%)	(39.2%, 74.5%)
95% CI for CR Rate [a]	(23.2%, 46.9%)	(17.5%, 41.4%)	(23.5%, 40.3%)	(22.9%, 57.9%)
95% CI for PR Rate [a]	(9.6%, 29.2%)	(13.4%, 36.0%)	(13.8%, 28.5%)	(7.0%, 35.5%)
Disease Control Rate (DCR: CR/PR/SD)	40 (59.7%)	36 (60.0%)	76 (59.8%)	21 (63.6%)
95% CI for DCR [a]	(47.0%, 71.5%)	(46.5%, 72.4%)	(50.8%, 68.4%)	(45.1%, 79.6%)

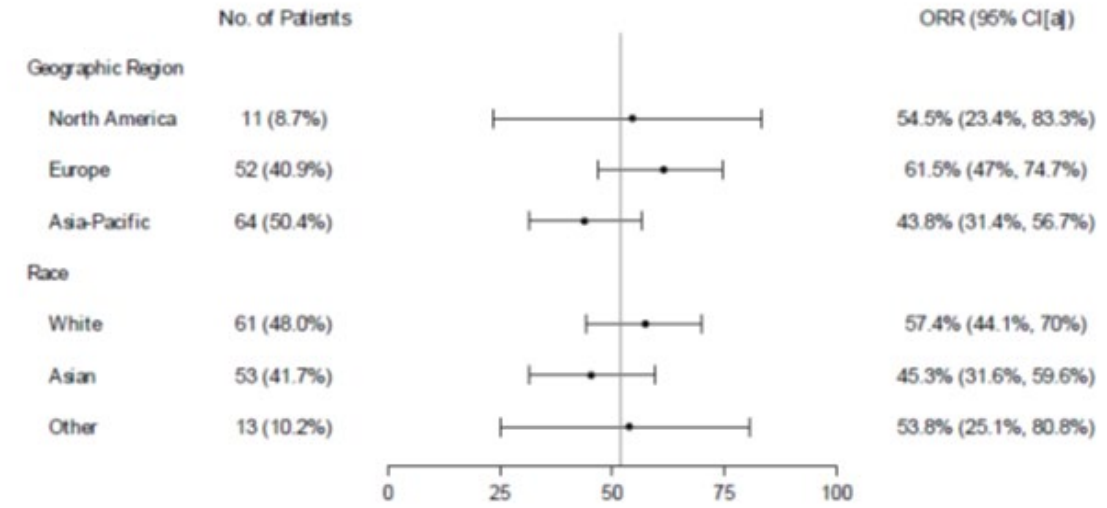
Data cut-off as of Oct 20th, 2023.
Patients who had opportunity for response assessment at 12 weeks exclude patients:
1) who started study drug <77 days prior to data cut off;
2) who started study drug >=77 days and <=91 days prior to cut off, and i) did not die, and ii) did not EOT (due to PD, loss to follow-up, withdrew consent) and EOS, and iii) did not have a tumor assessment within this window.
[a] Clopper-Person exact confidence interval.

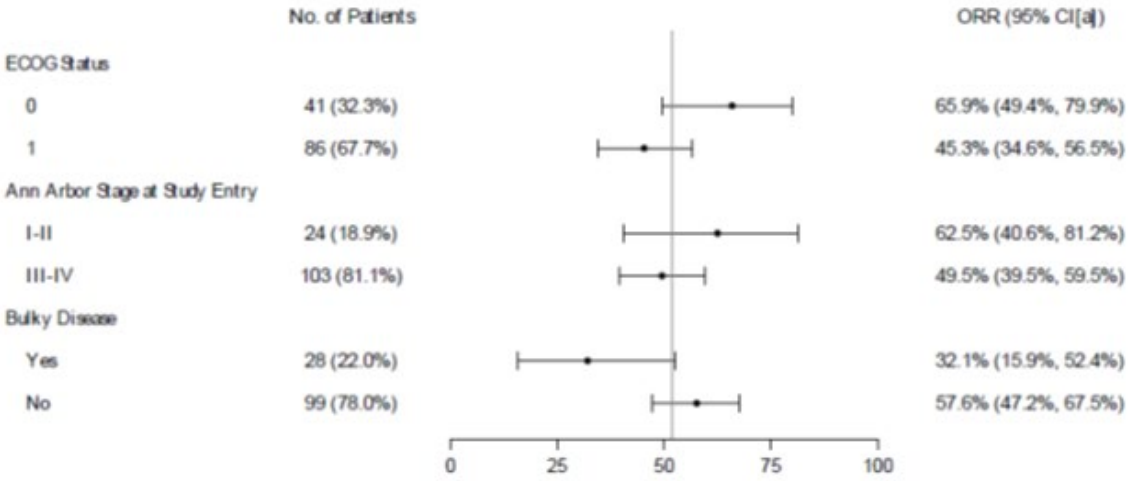
The proportion of patients with best response of PD was similar between the 2 regimens in patients with DLBCL.

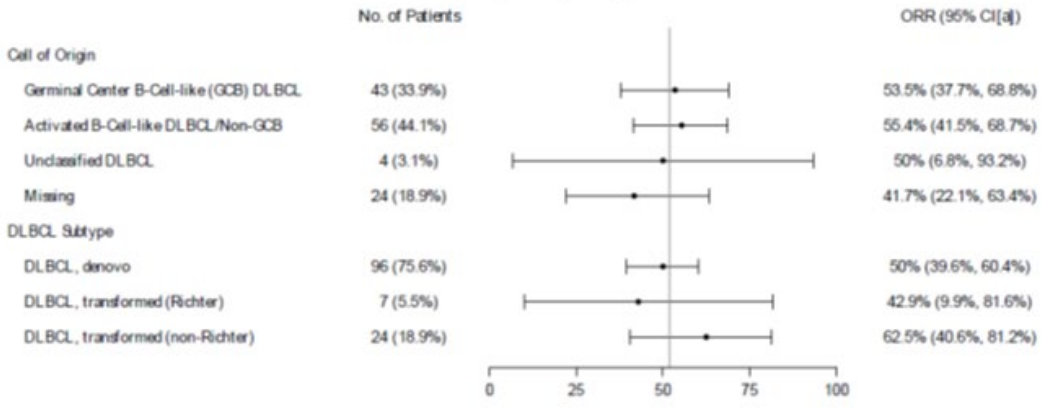
Subgroup analysis for ORR is presented in figure below by DCO 20 Oct 2023.

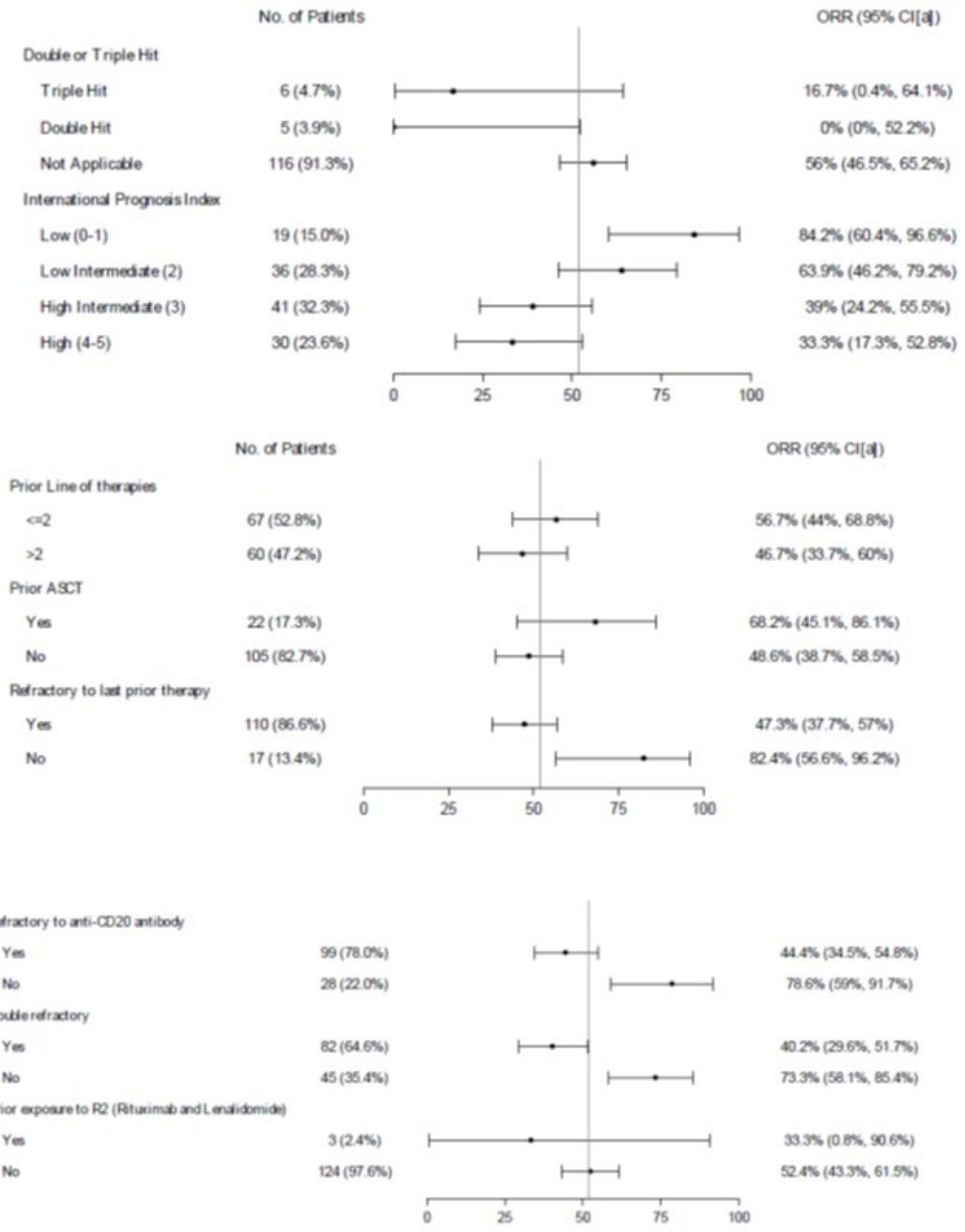
Figure 12 Forest plot for ORR by IRC DLBCL by DCO 20 Oct 2023




No. of Patients
ORR (95% CI[a])
Geographic Region
North America 11 (8.7%) 54.5% (23.4%, 83.3%)
Europe 52 (40.9%) 61.5% (47%, 74.7%)
Asia-Pacific 64 (50.4%) 43.8% (31.4%, 56.7%)
Race
White 61 (48.0%) 57.4% (44.1%, 70%)
Asian 53 (41.7%) 45.3% (31.6%, 59.6%)
Other 13 (10.2%) 53.8% (25.1%, 80.8%)
0 25 50 75 100


No. of Patients
ORR (95% CI[a])
ECOG Status
0 41 (32.3%) 65.9% (49.4%, 79.9%)
1 86 (67.7%) 45.3% (34.6%, 56.5%)
Ann Arbor Stage at Study Entry
I-II 24 (18.9%) 62.5% (40.6%, 81.2%)
III-IV 103 (81.1%) 49.5% (39.5%, 59.5%)
Bulky Disease
Yes 28 (22.0%) 32.1% (15.9%, 52.4%)
No 99 (78.0%) 57.6% (47.2%, 67.5%)
0 25 50 75 100


No. of Patients
ORR (95% CI[a])
Cell of Origin
Germinal Center B-Cell-like (GCB) DLBCL 43 (33.9%) 53.5% (37.7%, 68.8%)
Activated B-Cell-like DLBCL/Non-GCB 56 (44.1%) 55.4% (41.5%, 68.7%)
Unclassified DLBCL 4 (3.1%) 50% (6.8%, 93.2%)
Missing 24 (18.9%) 41.7% (22.1%, 63.4%)
DLBCL Subtype
DLBCL, denovo 96 (75.6%) 50% (39.6%, 60.4%)
DLBCL, transformed (Richter) 7 (5.5%) 42.9% (9.9%, 81.6%)
DLBCL, transformed (non-Richter) 24 (18.9%) 62.5% (40.6%, 81.2%)
0 25 50 75 100



At the updated DCO 20 Oct 2023, ORR (primary endpoint, n=127) was 52% (95% CI 43, 61), with a CR rate in 32% (95% CI 24, 40) of the patients. This is considered clinically relevant in patients with r/r DLBCL after 2 prior lines of therapy.

The lower bound of the 95% CI for ORR exceeded the 35% rate prespecified ORR in the SAP, which was chosen by the applicant as the minimum clinically meaningful ORR for the DLBCL cohort.

Despite the single-arm study design and limited sample size, activity of odronextamab is evident and can be isolated. Spontaneous remissions are not expected in r/r DLBCL after 2 prior lines of therapy.

Fourteen patients in the 1/20 mg cohort were not evaluable for primary endpoint due to discontinued study treatment before the opportunity for first post-baseline tumour assessment at week 12 because of progressive disease (n=4), withdrawal of consent (n=5), adverse events (n=4), or death (n=1). Fourteen patients in the 0.7/4/20 mg cohort discontinued study treatment before the opportunity for first post-baseline tumour assessment at week 12 because of death (n=9), adverse event (n=1),

progressive disease (n=3), or withdrawal of consent (n=1). All patients with progressive disease were based on local investigator clinical assessment, not radiological assessment. These subjects are adequately considered as failures in the primary endpoint ORR analyses of ORR.

According to the subgroup analysis, the ORR results are not considered to be driven by a specific subgroup. However, numerically lower ORR rates are noted in patients with bulky disease and double/triple-hit lymphoma, which may be expected.

Secondary endpoints

Table 32 Response rate per Investigator by DCO 20 Oct 2023

DLBCL Patients Who Had Opportunity for Response Assessment at 12 Weeks by Step-up Regimen and Dose

	DLBCL 1/20/160 mg (N=67)	DLBCL 0.7/4/20/160 mg (N=60)	Subtotal for DLBCL 160 mg (N=127)	DLBCL 1/20/320 mg (N=33)
Best Overall Tumor Response, n (%)				
Complete Response (CR)	30 (44.8%)	19 (31.7%)	49 (38.6%)	14 (42.4%)
Partial Response (PR)	5 (7.5%)	9 (15.0%)	14 (11.0%)	6 (18.2%)
Stable Disease (SD)	3 (4.5%)	5 (8.3%)	8 (6.3%)	1 (3.0%)
Progressive Disease (PD)	15 (22.4%)	11 (18.3%)	26 (20.5%)	6 (18.2%)
Not Evaluable (NE)	14 (20.9%)	16 (26.7%)	30 (23.6%)	6 (18.2%)
Response				
Objective Response Rate (ORR:CR+PR)	35 (52.2%)	28 (46.7%)	63 (49.6%)	20 (60.6%)
95% CI for ORR [a]	(39.7%, 64.6%)	(33.7%, 60.0%)	(40.6%, 58.6%)	(42.1%, 77.1%)
95% CI for CR Rate [a]	(32.6%, 57.4%)	(20.3%, 45.0%)	(30.1%, 47.6%)	(25.5%, 60.8%)
95% CI for PR Rate [a]	(2.5%, 16.6%)	(7.1%, 26.6%)	(6.2%, 17.8%)	(7.0%, 35.5%)
Disease Control Rate (DCR: CR/PR/SD)	38 (56.7%)	33 (55.0%)	71 (55.9%)	21 (63.6%)
95% CI for DCR [a]	(44.0%, 68.8%)	(41.6%, 67.9%)	(46.8%, 64.7%)	(45.1%, 79.6%)

Data cut-off as of Oct 20th, 2023.

CI, Confidence interval; CR, Complete response; DCR, Disease control rate; DLBCL, Diffuse large B-cell lymphoma; NE, Not evaluable; ORR, Objective response rate; PD, Progressive disease; PR, Partial response; SD, Stable disease.

There was concordance in the **overall response rates noted by investigator assessment** and IRC.

The CR rate per investigator assessment (49 [38.6%]) was numerically higher than the CR rate per IRC (40 [31.5%]); however, the 95% confidence intervals for CR broadly overlap.

Table 33 Duration of Response and Duration of Complete response per IRC by updated DCO 20 Oct 2023

Table 14.2.1.5.ed Kaplan-Meier Estimation of Duration of Response based on Lugano Classification per Independent Central Reviewers
(Full Analysis Set)
DLBCL Patients with CR/PR Who Had Opportunity for Response Assessment at 12 Weeks by Step-up Regimen and Dose

	DLBCL 1/20/160 mg (N=35)	DLBCL 0.7/4/20/160 mg (N=31)	Subtotal for DLBCL 160 mg (N=66)	DLBCL 1/20/320 mg (N=19)
KM Estimation of Duration of Response (CR or PR) (months) [a]				
n	35	31	66	19
Number of events, n (%)	19 (54.3%)	21 (67.7%)	40 (60.6%)	16 (84.2%)
Progressive Disease per Lugano, n (%)	8 (22.9%)	13 (41.9%)	21 (31.8%)	9 (47.4%)
Death, n (%)	11 (31.4%)	8 (25.8%)	19 (28.8%)	7 (36.8%)
Number of censored patients, n (%)	16 (45.7%)	10 (32.3%)	26 (39.4%)	3 (15.8%)
Median (95% CI), (months)	17.9 (5.4, NE)	8.6 (3.3, 13.9)	10.5 (5.0, 24.8)	20.6 (3.8, 32.3)

Data cut-off as of Oct 20th, 2023.
Patients who had opportunity for response assessment at 12 weeks exclude patients:
1) who started study drug <77 days prior to data cut off;
2) who started study drug >=77 days and <=91 days prior to cut off, and i) did not die, and ii) did not EOT (due to PD, loss to follow-up, withdrew consent) and EOS, and iii) did not have a tumor assessment within this window.
[a] Based on patients with CR or PR.

Table 14.2.1.5.ed Kaplan-Meier Estimation of Duration of Response based on Lugano Classification per Independent Central Reviewers
(Full Analysis Set)
DLBCL Patients with CR/PR Who Had Opportunity for Response Assessment at 12 Weeks by Step-up Regimen and Dose

	DLBCL 1/20/160 mg (N=35)	DLBCL 0.7/4/20/160 mg (N=31)	Subtotal for DLBCL 160 mg (N=66)	DLBCL 1/20/320 mg (N=19)
Estimated Event-Free Probability , % (95% CI)[a]				
3 months	78.6 (60.2, 89.2)	70.7 (51.2, 83.6)	74.9 (62.2, 83.8)	77.8 (51.1, 91.0)
6 months	66.0 (47.0, 79.6)	50.5 (31.8, 66.6)	58.6 (45.4, 69.6)	66.7 (40.4, 83.4)
9 months	62.9 (43.9, 77.0)	43.8 (25.9, 60.3)	53.6 (40.5, 65.0)	66.7 (40.4, 83.4)
12 months	59.6 (40.7, 74.2)	36.7 (20.0, 53.6)	48.5 (35.5, 60.2)	61.1 (35.3, 79.2)
15 months	56.1 (37.2, 71.3)	24.5 (9.3, 43.5)	42.1 (29.3, 54.4)	55.6 (30.5, 74.8)
18 months	49.1 (30.7, 65.1)	24.5 (9.3, 43.5)	37.5 (24.8, 50.1)	50.0 (25.9, 70.1)
21 months	49.1 (30.7, 65.1)	NE (NE, NE)	37.5 (24.8, 50.1)	50.0 (25.9, 70.1)
24 months	49.1 (30.7, 65.1)	NE (NE, NE)	37.5 (24.8, 50.1)	50.0 (25.9, 70.1)
27 months	45.6 (27.5, 61.9)	NE (NE, NE)	34.8 (22.2, 47.6)	37.0 (15.4, 59.0)
30 months	41.8 (24.2, 58.5)	NE (NE, NE)	31.9 (19.5, 45.0)	29.6 (10.2, 52.3)
33 months	41.8 (24.2, 58.5)	NE (NE, NE)	31.9 (19.5, 45.0)	22.2 (5.9, 45.0)
36 months	41.8 (24.2, 58.5)	NE (NE, NE)	31.9 (19.5, 45.0)	0.0 (NE, NE)
39 months	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	0.0 (NE, NE)

Data cut-off as of Oct 20th, 2023.
Patients who had opportunity for response assessment at 12 weeks exclude patients:
1) who started study drug <77 days prior to data cut off;
2) who started study drug >=77 days and <=91 days prior to cut off, and i) did not die, and ii) did not EOT (due to PD, loss to follow-up, withdrew consent) and EOS, and iii) did not have a tumor assessment within this window.
[a] Based on patients with CR or PR.

Table 14.2.1.15.ed Kaplan-Meier Estimation of Duration of Complete Response based on Lugano Classification per Independent Central Reviewers
(Full Analysis Set)
DLBCL Patients with CR Who Had Opportunity for Response Assessment at 12 Weeks by Step-up Regimen and Dose

	DLBCL 1/20/160 mg (N=23)	DLBCL 0.7/4/20/160 mg (N=17)	Subtotal for DLBCL 160 mg (N=40)	DLBCL 1/20/320 mg (N=13)
KM Estimation of Duration of Complete Response (CR) (months) [a]				
n	23	17	40	13
Number of events, n (%)	11 (47.8%)	9 (52.9%)	20 (50.0%)	11 (84.6%)
Progressive Disease per Lugano, n (%)	3 (13.0%)	2 (11.8%)	5 (12.5%)	6 (46.2%)
Death, n (%)	8 (34.8%)	7 (41.2%)	15 (37.5%)	5 (38.5%)
Number of censored patients, n (%)	12 (52.2%)	8 (47.1%)	20 (50.0%)	2 (15.4%)
Median (95% CI), (months)	36.3 (10.2, NE)	13.9 (4.1, NE)	17.9 (10.2, NE)	26.2 (2.8, 33.7)

Data cut-off as of Oct 20th, 2023.
Patients who had opportunity for response assessment at 12 weeks exclude patients:
1) who started study drug <77 days prior to data cut off;
2) who started study drug >=77 days and <=91 days prior to cut off, and i) did not die, and ii) did not EOT (due to PD, loss to follow-up, withdrew consent) and EOS, and iii) did not have a tumor assessment within this window.
[a] Based on patients with CR.

Table 14.2.1.15.ed Kaplan-Meier Estimation of Duration of Complete Response based on Lugano Classification per Independent Central Reviewers
(Full Analysis Set)
DLBCL Patients with CR Who Had Opportunity for Response Assessment at 12 Weeks by Step-up Regimen and Dose

	DLBCL 1/20/160 mg (N=23)	DLBCL 0.7/4/20/160 mg (N=17)	Subtotal for DLBCL 160 mg (N=40)	DLBCL 1/20/320 mg (N=13)
Estimated Event-Free Probability , % (95% CI)[a]				
3 months	87.0 (64.8, 95.6)	88.2 (60.6, 96.9)	87.5 (72.5, 94.6)	76.9 (44.2, 91.9)
6 months	73.9 (50.9, 87.3)	70.6 (43.1, 86.6)	72.5 (55.9, 83.7)	69.2 (37.3, 87.2)
9 months	73.9 (50.9, 87.3)	64.7 (37.7, 82.3)	69.9 (53.1, 81.7)	69.2 (37.3, 87.2)
12 months	69.3 (46.1, 84.0)	52.3 (26.8, 72.7)	61.9 (44.9, 75.1)	69.2 (37.3, 87.2)
15 months	64.3 (41.0, 80.4)	39.2 (13.0, 65.1)	55.2 (37.8, 69.6)	69.2 (37.3, 87.2)
18 months	54.4 (31.7, 72.5)	39.2 (13.0, 65.1)	47.9 (30.4, 63.4)	61.5 (30.8, 81.8)
21 months	54.4 (31.7, 72.5)	NE (NE, NE)	47.9 (30.4, 63.4)	61.5 (30.8, 81.8)
24 months	54.4 (31.7, 72.5)	NE (NE, NE)	47.9 (30.4, 63.4)	53.8 (24.8, 76.0)
27 months	54.4 (31.7, 72.5)	NE (NE, NE)	47.9 (30.4, 63.4)	43.1 (15.6, 68.3)
30 months	54.4 (31.7, 72.5)	NE (NE, NE)	47.9 (30.4, 63.4)	43.1 (15.6, 68.3)
33 months	54.4 (31.7, 72.5)	NE (NE, NE)	47.9 (30.4, 63.4)	32.3 (8.6, 59.4)
36 months	54.4 (31.7, 72.5)	NE (NE, NE)	47.9 (30.4, 63.4)	0.0 (NE, NE)
39 months	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	0.0 (NE, NE)

Data cut-off as of Oct 20th, 2023.
Patients who had opportunity for response assessment at 12 weeks exclude patients:
1) who started study drug <77 days prior to data cut off;
2) who started study drug >=77 days and <=91 days prior to cut off, and i) did not die, and ii) did not EOT (due to PD, loss to follow-up, withdrew consent) and EOS, and iii) did not have a tumor assessment within this window.
[a] Based on patients with CR.

Of the 18 DLBCL patients who transitioned to Q4W, 3 patients had PD after the transition and the estimated median duration of response from time of transition was NE (6.0, NE) with a median duration of follow-up from the of transition of 19.8 months (95% CI: 3.2, 25.8), by DCO 20 Oct 2023. Two of the 18 DLBCL that transitioned to Q4W had low or negative CD20 score of which none progressed after transition. Sixteen patients had unknown CD20 status of which 3 patients progressed after transition.

Table 34 Time to Response and Time to Complete response per IRC by updated DCO 20 Oct 2023

Table 14.2.1.29.ed Observed Time to Response based on Lugano Classification per Independent Central Reviewers
(Full Analysis Set)
DLBCL Patients with CR/PR Who Had Opportunity for Response Assessment at 12 Weeks by Step-up Regimen and Dose

	DLBCL 1/20/160 mg (N=35)	DLBCL 0.7/4/20/160 mg (N=31)	Subtotal for DLBCL 160 mg (N=66)	DLBCL 1/20/320 mg (N=19)
Observed Time to Response (CR or PR) (months) [a]				
n	35	31	66	19
Mean (SD)	2.66 (0.726)	2.67 (0.774)	2.67 (0.743)	2.65 (0.300)
Median	2.56	2.56	2.56	2.56
Q1 : Q3	2.43 : 2.66	2.46 : 2.69	2.46 : 2.69	2.43 : 2.83
Min : Max	0.8 : 4.7	1.1 : 6.4	0.8 : 6.4	2.4 : 3.5
Observed Time to Response (CR or PR), n (%) [a]				
<6 weeks	1 (2.9%)	1 (3.2%)	2 (3.0%)	0
>=6 weeks and <3 months	30 (85.7%)	27 (87.1%)	57 (86.4%)	17 (89.5%)
>=3 months and <6 months	4 (11.4%)	2 (6.5%)	6 (9.1%)	2 (10.5%)
>=6 months and <9 months	0	1 (3.2%)	1 (1.5%)	0
>=9 months	0	0	0	0

Data cut-off as of Oct 20th, 2023.
Patients who had opportunity for response assessment at 12 weeks exclude patients:
1) who started study drug <77 days prior to data cut off;
2) who started study drug >=77 days and <=91 days prior to cut off, and i) did not die, and ii) did not EOT (due to PD, loss to follow-up, withdrew consent) and EOS, and iii) did not have a tumor assessment within this window.
[a] Based on patients with CR or PR.

Table 14.2.1.33.ed Observed Time to Complete Response baseLugano Classification per Indepencependent Central Reviewers
(Full Analysis Set)
DLBCL Patients with CR Who Had Opportunity for Response Assessment at 12 Weeks by Step-up Regimen and Dose

	DLBCL 1/20/160 mg (N=23)	DLBCL 0.7/4/20/160 mg (N=17)	Subtotal for DLBCL 160 mg (N=40)	DLBCL 1/20/320 mg (N=13)
Observed Time to Complete Response (CR) (months) [a]				
n	23	17	40	13
Mean (SD)	3.01 (1.311)	3.39 (1.650)	3.17 (1.457)	3.71 (2.454)
Median	2.56	2.63	2.58	2.60
Q1 : Q3	2.43 : 2.86	2.53 : 3.09	2.53 : 3.02	2.53 : 3.15
Min : Max	1.4 : 8.1	2.4 : 8.1	1.4 : 8.1	2.4 : 10.0
Observed Time to Complete Response (CR), n (%) [a]				
<6 weeks	0	0	0	0
>=6 weeks and <3 months	18 (78.3%)	11 (64.7%)	29 (72.5%)	9 (69.2%)
>=3 months and <6 months	4 (17.4%)	4 (23.5%)	8 (20.0%)	2 (15.4%)
>=6 months and <9 months	1 (4.3%)	2 (11.8%)	3 (7.5%)	1 (7.7%)
>=9 months and <12 months	0	0	0	1 (7.7%)
>=12 months	0	0	0	0

Data cut-off as of Oct 20th, 2023.
Patients who had opportunity for response assessment at 12 weeks exclude patients:
1) who started study drug <77 days prior to data cut off;
2) who started study drug >=77 days and <=91 days prior to cut off, and i) did not die, and ii) did not EOT (due to PD, loss to follow-up, withdrew consent) and EOS, and iii) did not have a tumor assessment within this window.
[a] Based on patients with CR.

The first response assessment per protocol was at week 12 (±7-day window), therefore quantification of **Time to response/Time to complete response** before that time was not possible.

Time to response and Time to complete response were similar between the two different step-up regimens, which points towards homogeneity in response. However, most responses (86.4%) were evident by the time of first response assessment at week 12. The median observed TTR was 2.6 months (range: 0.8 to 6.4). Further, most CRs (72.5%) were evident by the time of first response assessment, and median observed TTCR was 2.6 months (range 1.4 to 8.1).

Secondary endpoint **PFS**

Table 35 PFS per IRC by DCO 20 Oct 2023

Table 14.2.3.1.ed Progression-free Survival per Independent Central Reviewers
(Full Analysis Set)
DLBCL Patients Who Had Opportunity for Response Assessment at 12 Weeks by Step-up Regimen and Dose

	DLBCL 1/20/160 mg (N=67)	DLBCL 0.7/4/20/160 mg (N=60)	Subtotal for DLBCL 160 mg (N=127)	DLBCL 1/20/320 mg (N=33)
Number of events, n (%)	45 (67.2%)	47 (78.3%)	92 (72.4%)	26 (78.8%)
Progressive Disease per Lugano, n (%)	25 (37.3%)	23 (38.3%)	48 (37.8%)	17 (51.5%)
Death, n (%)	20 (29.9%)	24 (40.0%)	44 (34.6%)	9 (27.3%)
Number of censored patients, n (%)	22 (32.8%)	13 (21.7%)	35 (27.6%)	7 (21.2%)
Median (95% CI), (months)	4.7 (3.8, 9.6)	4.3 (2.7, 5.8)	4.4 (3.6, 5.9)	6.6 (3.4, 19.4)

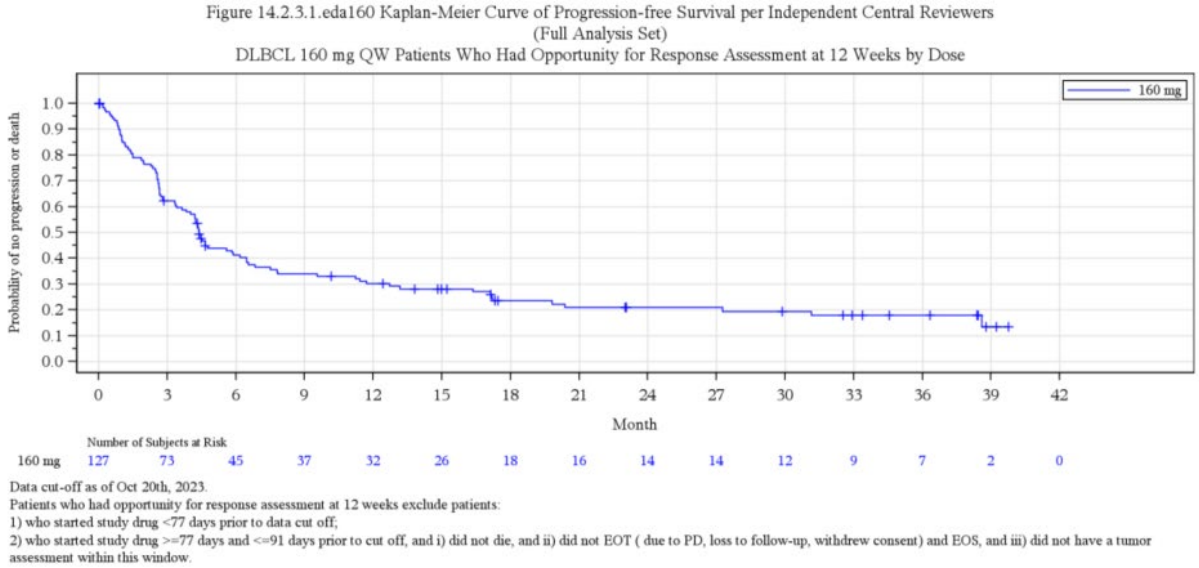
Data cut-off as of Oct 20th, 2023.
Patients who had opportunity for response assessment at 12 weeks exclude patients:
1) who started study drug <77 days prior to data cut off,
2) who started study drug >=77 days and <=91 days prior to cut off, and i) did not die, and ii) did not EOT (due to PD, loss to follow-up, withdrew consent) and EOS, and iii) did not have a tumor assessment within this window.
[a] Based on Kaplan-Meier method.

Table 14.2.3.1.ed Progression-free Survival per Independent Central Reviewers
(Full Analysis Set)
DLBCL Patients Who Had Opportunity for Response Assessment at 12 Weeks by Step-up Regimen and Dose

	DLBCL 1/20/160 mg (N=67)	DLBCL 0.7/4/20/160 mg (N=60)	Subtotal for DLBCL 160 mg (N=127)	DLBCL 1/20/320 mg (N=33)
Estimated Event-Free Probability , % (95% CI)[a]				
3 months	68.9 (55.6, 78.9)	55.2 (41.5, 66.9)	62.2 (52.8, 70.2)	72.4 (52.3, 85.1)
6 months	45.3 (32.4, 57.3)	37.0 (24.7, 49.4)	41.2 (32.2, 50.0)	50.7 (31.3, 67.2)
9 months	38.1 (25.8, 50.2)	29.6 (18.3, 41.8)	33.9 (25.4, 42.6)	43.4 (25.1, 60.5)
12 months	36.2 (24.2, 48.4)	24.1 (13.8, 35.9)	30.1 (22.0, 38.7)	43.4 (25.1, 60.5)
15 months	34.3 (22.5, 46.5)	22.1 (12.2, 33.7)	28.2 (20.2, 36.7)	39.8 (22.1, 57.1)
18 months	32.3 (20.7, 44.5)	13.2 (5.1, 25.2)	23.6 (16.0, 32.0)	36.2 (19.2, 53.5)
21 months	28.3 (17.2, 40.4)	13.2 (5.1, 25.2)	21.0 (13.6, 29.4)	32.6 (16.4, 49.8)
24 months	28.3 (17.2, 40.4)	NE (NE, NE)	21.0 (13.6, 29.4)	32.6 (16.4, 49.8)
27 months	28.3 (17.2, 40.4)	NE (NE, NE)	21.0 (13.6, 29.4)	29.0 (13.8, 46.1)
30 months	26.3 (15.5, 38.3)	NE (NE, NE)	19.5 (12.3, 27.9)	24.8 (10.7, 41.9)
33 months	24.1 (13.7, 36.1)	NE (NE, NE)	17.8 (10.8, 26.4)	19.9 (7.2, 37.1)
36 months	24.1 (13.7, 36.1)	NE (NE, NE)	17.8 (10.8, 26.4)	14.9 (4.2, 31.9)
39 months	18.0 (7.2, 32.9)	NE (NE, NE)	13.4 (5.6, 24.5)	0.0 (NE, NE)
42 months	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	0.0 (NE, NE)

Data cut-off as of Oct 20th, 2023.
Patients who had opportunity for response assessment at 12 weeks exclude patients:
1) who started study drug <77 days prior to data cut off,
2) who started study drug >=77 days and <=91 days prior to cut off, and i) did not die, and ii) did not EOT (due to PD, loss to follow-up, withdrew consent) and EOS, and iii) did not have a tumor assessment within this window.
[a] Based on Kaplan-Meier method.

Figure 13 PFS per IRC by DCO 20 Oct 2023



By updated DCO 20 Oct 2023, the median PFS was the same as by DCO 31 Jan 2023.

Secondary endpoint **OS**

Table 36 OS by DCO 20 Oct 2023

Table 14.2.2.1.ed Overall Survival
(Full Analysis Set)
DLBCL Patients Who Had Opportunity for Response Assessment at 12 Weeks by Step-up Regimen and Dose

	DLBCL 1/20/160 mg (N=67)	DLBCL 0.7/4/20/160 mg (N=60)	Subtotal for DLBCL 160 mg (N=127)	DLBCL 1/20/320 mg (N=33)
Number of deaths, n (%)	41 (61.2%)	39 (65.0%)	80 (63.0%)	22 (66.7%)
Number of censored patients, n (%)	26 (38.8%)	21 (35.0%)	47 (37.0%)	11 (33.3%)
Median (95% CI), (months)[a]	9.6 (7.1, 19.8)	7.9 (4.4, 15.3)	9.2 (6.5, 12.7)	19.3 (8.1, 34.9)

Data cut-off as of Oct 20th, 2023.
Patients who had opportunity for response assessment at 12 weeks exclude patients:
1) who started study drug <77 days prior to data cut off,
2) who started study drug >=77 days and <=91 days prior to cut off, and i) did not die, and ii) did not EOT (due to PD, loss to follow-up, withdrew consent) and EOS, and iii) did not have a tumor assessment within this window.
[a] Based on Kaplan-Meier method.

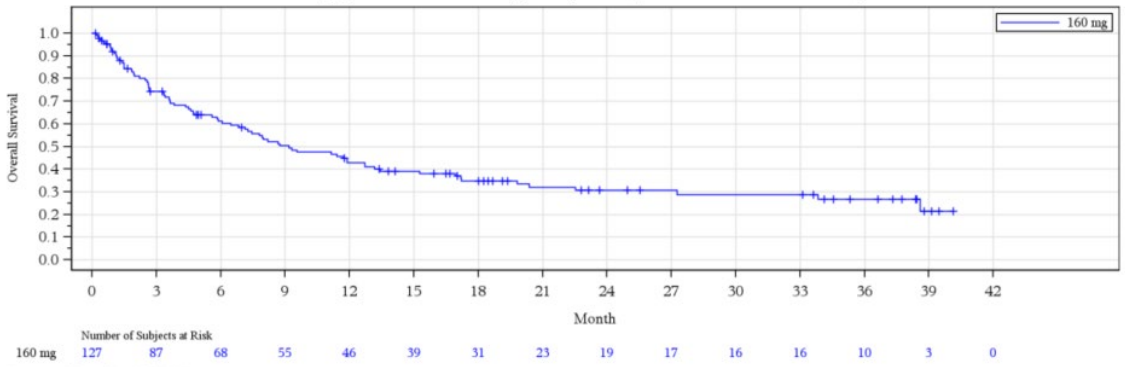
Table 14.2.2.1.ed Overall Survival
(Full Analysis Set)
DLBCL Patients Who Had Opportunity for Response Assessment at 12 Weeks by Step-up Regimen and Dose

	DLBCL 1/20/160 mg (N=67)	DLBCL 0.7/4/20/160 mg (N=60)	Subtotal for DLBCL 160 mg (N=127)	DLBCL 1/20/320 mg (N=33)
Estimated Survival Probability , % (95% CI)[a]				
3 months	77.7 (65.2, 86.1)	70.7 (57.1, 80.6)	74.3 (65.5, 81.2)	87.1 (69.1, 95.0)
6 months	64.1 (50.7, 74.7)	58.2 (44.4, 69.7)	61.2 (51.8, 69.4)	79.8 (60.4, 90.4)
9 months	53.1 (39.6, 64.9)	47.3 (33.9, 59.6)	50.3 (40.8, 59.0)	69.0 (48.6, 82.6)
12 months	43.8 (30.7, 56.1)	41.8 (28.9, 54.2)	42.9 (33.7, 51.8)	65.3 (45.0, 79.7)
15 months	40.0 (27.2, 52.4)	38.2 (25.6, 50.6)	39.2 (30.2, 48.1)	50.8 (31.4, 67.3)
18 months	38.0 (25.4, 50.5)	31.2 (19.2, 43.9)	34.8 (26.0, 43.8)	50.8 (31.4, 67.3)
21 months	34.0 (21.9, 46.5)	31.2 (19.2, 43.9)	32.1 (23.3, 41.2)	43.6 (25.1, 60.7)
24 months	34.0 (21.9, 46.5)	26.0 (13.3, 40.6)	30.7 (21.9, 39.8)	43.6 (25.1, 60.7)
27 months	34.0 (21.9, 46.5)	NE (NE, NE)	30.7 (21.9, 39.8)	43.6 (25.1, 60.7)
30 months	32.0 (20.1, 44.5)	NE (NE, NE)	28.9 (20.1, 38.2)	39.2 (21.3, 56.7)
33 months	32.0 (20.1, 44.5)	NE (NE, NE)	28.9 (20.1, 38.2)	34.8 (17.7, 52.7)
36 months	29.7 (18.1, 42.2)	NE (NE, NE)	26.8 (17.9, 36.5)	30.5 (14.3, 48.4)
39 months	23.8 (11.2, 38.9)	NE (NE, NE)	21.4 (10.9, 34.3)	20.9 (7.5, 38.9)
42 months	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	0.0 (NE, NE)

Data cut-off as of Oct 20th, 2023.
Patients who had opportunity for response assessment at 12 weeks exclude patients:
1) who started study drug <77 days prior to data cut off,
2) who started study drug >=77 days and <=91 days prior to cut off, and i) did not die, and ii) did not EOT (due to PD, loss to follow-up, withdrew consent) and EOS, and iii) did not have a tumor assessment within this window.
[a] Based on Kaplan-Meier method.

Figure 14 OS by DCO 20 Oct 2023

Figure 14.2.2.1.eda160 Kaplan-Meier Curve of Overall Survival
(Full Analysis Set)
DLBCL 160 mg QW Patients Who Had Opportunity for Response Assessment at 12 Weeks by Dose



Number of Subjects at Risk

160 mg	127	87	68	55	46	39	31	23	19	17	16	16	10	3	0

Data cut-off as of Oct 20th, 2023.
Patients who had opportunity for response assessment at 12 weeks exclude patients:
1) who started study drug <77 days prior to data cut off;
2) who started study drug >=77 days and <=91 days prior to cut off, and i) did not die, and ii) did not EOT (due to PD, loss to follow-up, withdrew consent) and EOS, and iii) did not have a tumor assessment within this window.

By updated DCO 20 Oct 2023, the median OS was 9.2 months (95% CI 6.5 to 12.7)

PFS and OS (secondary endpoints) are time dependent endpoints that do not isolate drug effects in a single-arm trial.

No thorough assessment was performed of the PRO methodology or results.

- **Ancillary analyses**

  N/A

- **Summary of main efficacy results**

The following table summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 37 Summary of efficacy for trial 1625 FL and DLBCL as of DCO 20 Oct 2023

Title: An Open-Label Study to Assess the Anti-Tumour Activity and Safety of REGN1979, an anti-CD20 x anti-CD3 Bispecific Antibody, in Patients with Relapsed or Refractory B-cell non-Hodgkin Lymphoma		
Study identifier	R1979-ONC-1625, ELM-2, EudraCT Number 2017-002139-41 (the study transitioned to EU CTR and EU CT number is 2024-511747-25-00), NCT03888105, IND Number 120417.	
Design	Single-arm, open-label, multicohort, multicentre, phase 2 study	
	Duration of main phase:	Study initiation date 20 Nov 2019 (ongoing)
	Duration of Run-in phase:	Not applicable.
	Duration of Extension phase:	Not applicable.

Title: An Open-Label Study to Assess the Anti-Tumour Activity and Safety of REGN1979, an anti-CD20 x anti-CD3 Bispecific Antibody, in Patients with Relapsed or Refractory B-cell non-Hodgkin Lymphoma			
Study identifier	R1979-ONC-1625, ELM-2, EudraCT Number 2017-002139-41 (the study transitioned to EU CTR and EU CT number is 2024-511747-25-00), NCT03888105, IND Number 120417.		
Hypothesis	Exploratory. For **FL**, a prespecified ORR of 49% was chosen by the applicant as the minimum clinically meaningful ORR. For **DLBCL**, a prespecified ORR of 35% was chosen by the applicant as the minimum clinically meaningful ORR.		
Treatments groups	**FL** and **DLBCL** cohorts		Initially, the 1/20 mg step-up regimen was used with 1 mg in week 1 (split as 0.5 mg on day 1 and 0.5 mg on day 2 of cycle 1), and 20 mg in week 2 (split as 10 mg on day 8 and 10 mg on day 9 of cycle 1). From protocol amendment 4, the 0.7/4/20 mg step-up dosing regimen was used with first 0.7 mg (split as 0.2 mg on cycle 1 day 1 and 0.5 mg on cycle 1 day 2), then 4 mg (split as 2 mg on cycle 1 day 8 and 2 mg on cycle 1 day 9), and then 20 mg (split as 10 mg on cycle 1 day 15 and 10 mg on cycle 1 day 16. Monotherapy odronextamab was administered IV, first in 4 cycles (each cycle 21-day) and then in a maintenance phase with Q2W dosing. If CR was maintained for 9 months, then odronextamab was to be administered every 4 weeks. For **FL** (n=128), 80 mg QW/160 mg Q2W followed by 160 mg Q4W was used. For **DLBCL** (n=127), 160 mg QW/320 mg Q2W followed by 320 mg Q4W was used. Odronextamab was given until disease progression or other protocol defined reason for treatment discontinuation.
Endpoints and definitions	Primary: Objective response rate by IRC	ORR by IRC	ORR according to the Lugano Classification (Cheson, 2014) by IRC. The ORR was assessed from the time of the first patient first dose until all patients have completed 52-week tumour assessment for **FL** and 36-week tumour assessment for **DLBCL** or have withdrawn from the study.
	Secondary: Complete response by IRC	CR by IRC	CR rate according to the Lugano Classification

Title: An Open-Label Study to Assess the Anti-Tumour Activity and Safety of REGN1979, an anti-CD20 x anti-CD3 Bispecific Antibody, in Patients with Relapsed or Refractory B-cell non-Hodgkin Lymphoma			
Study identifier	R1979-ONC-1625, ELM-2, EudraCT Number 2017-002139-41 (the study transitioned to EU CTR and EU CT number is 2024-511747-25-00), NCT03888105, IND Number 120417.		
	Secondary: Duration of Response by IRC	DoR by IRC	Time from the first documented CR or PR until the first date of progressive disease, or death due to any cause, whichever occurs first
	Secondary: Duration of Complete Response by IRC	DoCR by IRC	Time from the first documented CR until the first date of progressive disease, or death due to any cause, whichever occurs first
	Secondary: Time to response by IRC	TTR by IRC	Time from the first dose to the date of first documented CR/PR
Database lock	Database lock on 23 March 2023 for DCO 31 Jan 2023 (Interim Analysis for FL, Primary Analysis for DLBCL) Database lock on 15 Dec 2023 for DCO 20 October 2023 (Primary analysis of FL, updated analyses of DLBCL cohort)		
Results and Analysis			
Analysis description	31 Jan 2023 is the Data cutoff for the **Interim analysis of FL cohort** and for the **Primary analysis of DLBCL cohort**. Data cut-off for Primary analysis of FL cohort and updated analyses of DLBCL cohort: 20 Oct 2023		
Analysis population and time point description	Full analysis set (FAS) included all enrolled patients who received any doses of odronextamab. Efficacy Analysis Set (EAS) included all enrolled patients who received any dose of odronextamab and had the opportunity for efficacy assessment at 12 weeks. An interim analysis was to be conducted when 80 patients with FL had completed 52-week assessment and 127 patients in the DLBCL cohort had completed 36-week assessment or have withdrawn from the study, whichever was later. With amendment 2, the interim analysis was removed for the DLBCL cohort. With amendment 4, the primary analysis was to be conducted when all patients with FL had completed 52-week tumour assessment and DLBCL patients had 36 week tumour assessment or had withdrawn from the study.		
Descriptive statistics and estimate variability by IRC	Treatment group	FL and DLBCL cohorts, as of DCO 20 Oct 2023	
	Number of subjects	**FL** n=128, **DLBCL** n=127	
	ORR, % (95% CI)	**FL** 80.5% (72.5%, 86.9%) **DLBCL** 52.0% (42.9%, 60.9%)	

Title: An Open-Label Study to Assess the Anti-Tumour Activity and Safety of REGN1979, an anti-CD20 x anti-CD3 Bispecific Antibody, in Patients with Relapsed or Refractory B-cell non-Hodgkin Lymphoma		
Study identifier	R1979-ONC-1625, ELM-2, EudraCT Number 2017-002139-41 (the study transitioned to EU CTR and EU CT number is 2024-511747-25-00), NCT03888105, IND Number 120417.	
	CR, % (95% CI)	**FL** 73.4% (64.9%, 80.9%) **DLBCL** 31.5% (23.5%, 40.3%)
	Median DoR* months (95% CI)	**FL** 22.6 (17.7, NE) **DLBCL** 10.5 (5.0, 24.8)
	Median DoCR* months (95% CI)	**FL** 25.1 (20.5, NE) **DLBCL** 17.9 (10.2, NE)
	Median TTR Months (range)	**FL** 2.7 (1.8-7.9) **DLBCL** 2.6 months (0.8-6.4)
Notes	* KM estimation	

2.6.5.3. Clinical studies in special populations

Table 38 Clinical studies in special populations

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
Controlled Trials	N/A	N/A	N/A
Non Controlled Trials	- FL 80 mg (1625+1333) (n=46/153) - DLBCL 160 mg (1625+1333) (n=76/219) - FL 80 mg + DLBCL 160 mg (1625+1333) (n=122/372)	- FL 80 mg (1625+1333) (n=16/153) - DLBCL 160 mg (1625+1333) (n=39/219) - FL 80 mg + DLBCL 160 mg (1625+1333) (n=55/372)	- FL 80 mg (1625+1333) (n=0/153) - DLBCL 160 mg (1625+1333) (n=4/219) - FL 80 mg + DLBCL 160 mg (1625+1333) (n=4/372)

2.6.5.4. In vitro biomarker test for patient selection for efficacy

N/A

2.6.5.5. Analysis performed across trials (pooled analyses and meta-analysis)

N/A

2.6.5.6. Supportive studies

2.6.5.6.1. Study 1333 – with a "prior CAR-T therapy DLBCL" cohort

According to the applicant, efficacy data for the proposed DLBCL indication are based upon data from patients with DLBCL without prior CAR-T in the pivotal study 1625, and, supported by data from study 1333 which included an expansion cohort of DLBCL patients who progressed after CAR-T therapy.

Study design

Study 1333 is a first-in-human, phase 1, open-label, multicenter, dose-finding and expansion study of odronextamab monotherapy in patients with CD20+ B-cell malignancies (B NHL and CLL) previously treated with anti-CD20 antibody therapy with both IV (Part A) and subcutaneous (Part B) administration. The study consisted of a dose escalation portion followed by disease-specific expansions.

The applicant states that during the dose-finding portion of study 1333, efficacy was observed in different B-NHL subtypes. Based on these observations, the antitumour activity and safety of odronextamab was further evaluated in 5 separate disease-specific cohorts in the pivotal study 1625, and also in a cohort of DLBCL patients in study 1333 who were relapsed or refractory to CAR-T therapy.

Figure 15 Design of study 1333

Figure 1: Study Schema

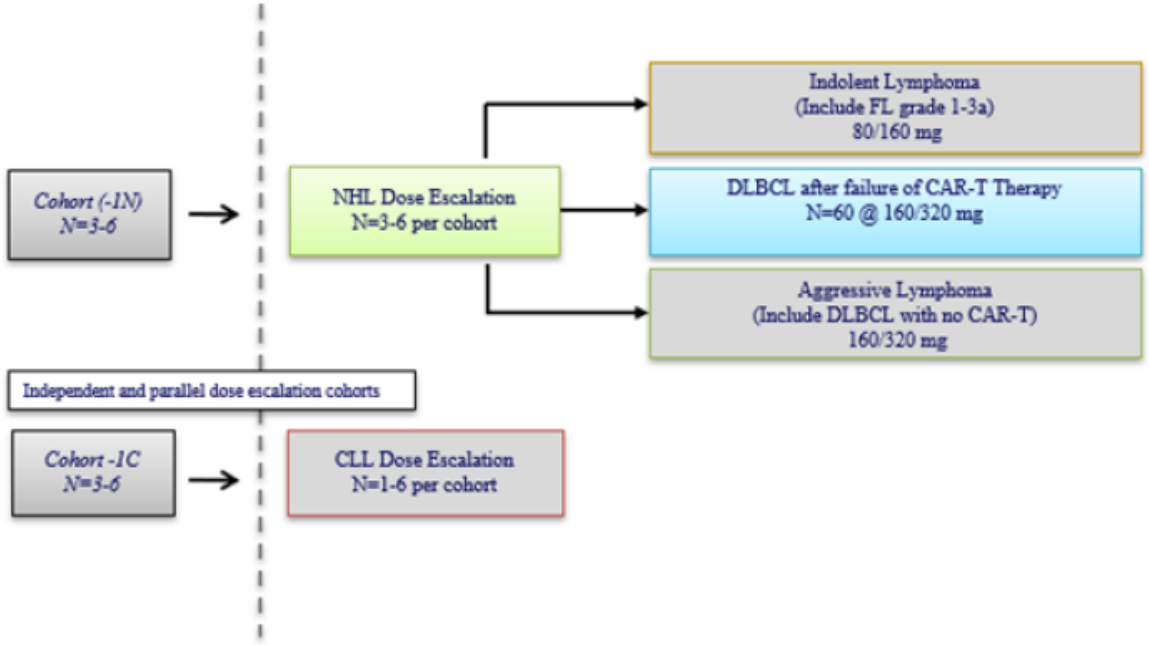
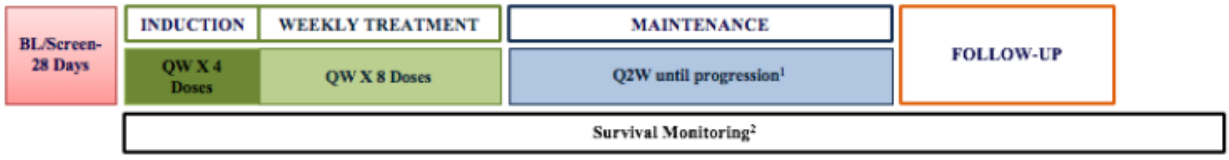


Figure 2: Current Study Flow Diagram for Disease-Specific Expansions



[1] Study treatment was to continue until time of disease progression or other protocol-defined reason for treatment discontinuation. If a patient had demonstrated a CR and had shown a durable response for at least 9 months after the initial determination of CR, then the frequency of study drug administration at the assigned dose was decreased from Q2W to Q4W intervals. Patients must have been receiving the full dose of Q2W dosing for at least 3 preceding doses before switching from Q2W to Q4W dosing.

[2] Patients who discontinued from follow-up but had not withdrawn consent continued survival follow-up until death, loss to follow-up, withdrawal of consent or study termination by the sponsor, whichever was earlier. Patients could be followed remotely for survival.

Study participants

Study 1333 enrolled patients with documented CD20+ B cell malignancy, with active disease not responsive to prior therapy, for whom no standard of care options exists, and for whom treatment with an anti-CD20 antibody could be appropriate. Patients with B-NHL must have had prior treatment with an anti-CD20 antibody therapy.

The key entry criteria for the disease-specific expansion cohort enrolling "DLBCL patients after CAR-T therapy", was that the patient should have recovered from the toxicities of the lymphodepletion therapy and CAR-T infusion. As with Study 1625, patients were not tested for CD20 expression for study entry.

Treatment

Extensive dose optimization occurred in the dose escalation phase and 17 dose levels ranging from 0.03 mg to 320 mg were tested, which included 13 different step-up increments tested at weeks 1 and 2 that informed the step-up dosing regimen in the dose expansion phase.

During the course of study 1333, a decision was taken to evaluate the selected RP2D in the phase 2 study 1625 and thus enrolment in study 1333 was closed in the FL and aggressive B-NHL expansion cohorts; but the DLBCL after CAR-T continued to enrol in study 1333.

According to the applicant, the treatment plan was revised over multiple amendments, as might be anticipated in a phase 1 study. After Amendment 13 (17 Dec 2019), patients received odronextamab QW for the first 12 doses (including step-up doses), followed by Q2W treatment until disease progression or other protocol-defined reason for treatment discontinuation. In addition, if a patient had demonstrated a CR for at least 9 months, the frequency was decreased from Q2W to Q4W intervals.

A discussed in other parts of this report, there was a pause in enrolment in Study 1625 and 1333, due to a partial clinical hold imposed by the FDA on 11 Dec 2020 due to the incidence of grade ≥3 CRS events observed in patients treated with 1/20 regimen in Studies 1333 and 1625. The Sponsor implemented a voluntary pause on both studies in other jurisdictions according to the local clinical study framework. The cohorts of FL, DLBCL, and other B-NHL in both studies resumed enrolment on 13 May 2021 following the removal of partial clinical hold by the FDA with an optimized step-up dosing regimen, enhanced premedication, updated guidance for the intervention with tocilizumab and steroids, and increased monitoring in the event of CRS in global protocol amendment 4 to Study 1625 and global protocol amendment 16 to Study 1333. To reduce the rate of grade 3 CRS, the 1/20 step-up regimen was changed to the 0.7/4/20 mg a step-up regimen of from Amendment 16 onwards in study 1333.

The odronextamab dosing for DLBCL with 1/20 or 0.7/4/20 step-up dosing regimen, in study 1333 expansion cohort and study 1625, is provided in table below.

Table 39 Dosing for DLBCL with 0.7/4/20 or 1/20 step-up regimen, cycles 1-4 were each 21 days.

Table 2: Odronextamab Dose and Schedule Evaluated for Efficacy for the Treatment of R/R DLBCL

Day of Treatment Cycle		Dose of IV Odronextamab (mg)	
		0.7/4/20 regimen (Proposed for registration)	1/20 regimen
Cycle 1 (Step Up)	Day 1	0.2	0.5
	Day 2	0.5	0.5
	Day 8	2	10
	Day 9	2	10
	Day 15	10	160
	Day 16	10	-
Cycles 2-4	Day 1	160	160
	Day 8	160	160
	Day 15	160	160
Maintenance (Every 2 Weeks)	Begin 1 week after end of Cycle 4	320	320

Initial dose will be 0.7 mg split as 0.2 mg on cycle 1 day 1 and 0.5 mg on cycle 1 day 2; intermediate dose 1 will be 4 mg (split as 2 mg on cycle 1 day 8 and 2 mg on cycle 1 day 9); intermediate dose 2 will be 20 mg (split as 10 mg on cycle 1 day 15 and 10 mg on cycle 1 day 16)
Note: If a patient has maintained CR for 9 months, then odronextamab will be administered every 4 weeks at the same dose.

The applicant has clarified that all 60 patients in the DLBCL after CAR-T cohort were treated according to the proposed dosing frequency.

Objectives/endpoints and statistical considerations

Figure 16 Selected part of Study Objectives and Endpoints for study 1333

2. STUDY OBJECTIVES (PART A)

The study objectives and endpoints for Part A are described below.

Objectives	Endpoints
Primary	
• To assess the safety, tolerability, and dose-limiting toxicities (DLTs) of odronextamab administered intravenously (IV).	• Safety (specifically, AEs and DLTs) to determine the MTD and/or OBD as RP2D of odronextamab
• To evaluate odronextamab concentrations in the aggressive lymphoma (excluding patients with prior CAR-T therapy) and FL grade 1-3a expansion cohorts that may correlate with observed toxicity and potential antitumor activity.	• Concentration of odronextamab in serum
• To study the antitumor activity of odronextamab in the DLBCL after failure of CAR-T therapy expansion cohort as assessed by independent central review	• ORR according to the Lugano Classification of response in malignant lymphoma (Cheson, 2014) and as assessed by independent central review in the DLBCL after failure of CAR-T therapy expansion cohort. The ORR was assessed from the time of the first patient first dose until all patients in this cohort had completed the 36-week tumor assessment or had withdrawn from the study
Secondary	
• To characterize the pharmacokinetic (PK) profile of odronextamab	• Concentration of odronextamab
• To assess the immunogenicity of odronextamab	• Anti-odronextamab antibodies and incidence of neutralizing antibodies (NAb) to odronextamab over time

In study 1333, there was no formal hypothesis test, and all the analyses were descriptive in nature.

The applicant has submitted the SAP version 2.0 dated 10 Jan 2022, which is based on protocol amendment 16 that was approved 14 May 2021. Major changes in SAP version 2.0 included Study design, Study plan and Sample size were updated per Protocol amendment 16, as stated by the applicant.

According to the submitted SAP, with a sample size of 60 patients in DLBCL after failure of CAR-T therapy, if the observed ORR is at least 31%, 38%, 43% and 48%, the lower limit of 95% CI will exclude the ORR of 20%, 26%, 30% and 35% respectively; i.e., the ORR will have been shown to be significantly different from 20%, 26%, 30% and 35%.

As of DCO 22 Jan 2024, all 60 patients in the FAS were efficacy evaluable and had the opportunity for 9 months of follow-up.

The FAS included all patients enrolled in the DLBCL after CAR-T cohort. The Efficacy Analysis Set in the "DLBCL After CAR-T Expansion Cohort" enrolled patients who received any dose of odronextamab and had the opportunity for efficacy assessment at 12 weeks.

Study population

At the data cutoff date (22 Jan 2024), treatment was ongoing for 2 patients of the 60 patients on-study who received treatment in the after CAR-T cohort in the FAS.

Table 40 Patient disposition DLBCL with prior CAR-T therapy by updated DCO 22 Jan 2024

Table 14.1.1.5.edtp Patient Disposition
(Full Analysis Set)
DLBCL Post CAR-T Failure Dose Expansion Patients Who Had Opportunity for Response Assessment at 12 Weeks by Step-up Regimen

	1/20/160 mg (N=20)	0.7/4/20/160 mg (N=40)	Total (N=60)
Treatment ongoing, n (%)	0	2 (5.0%)	2 (3.3%)
Off treatment, n (%)	20 (100%)	38 (95.0%)	58 (96.7%)
Treatment completed, n (%)	0	0	0
Treatment discontinued, n (%)	20 (100%)	38 (95.0%)	58 (96.7%)
Primary reason for treatment discontinuation			
ADVERSE EVENT	3 (15.0%)	4 (10.0%)	7 (11.7%)
DEATH	1 (5.0%)	1 (2.5%)	2 (3.3%)
PHYSICIAN DECISION	4 (20.0%)	8 (20.0%)	12 (20.0%)
PROGRESSIVE DISEASE	9 (45.0%)	24 (60.0%)	33 (55.0%)
WITHDRAWAL BY SUBJECT	3 (15.0%)	1 (2.5%)	4 (6.7%)

Data cut-off as of Jan 22nd 2024.
Patients who had opportunity for response assessment at 12 weeks exclude patients:
1) who started study drug <77 days prior to data cut off;
2) who started study drug >=77 days and <=91 days prior to cut off, and i) did not die, and ii) did not EOT (due to PD, loss to follow-up, withdrew consent) and EOS, and iii) did not have a tumor assessment within this window.

Table 14.1.1.5.edtp Patient Disposition
(Full Analysis Set)
DLBCL Post CAR-T Failure Dose Expansion Patients Who Had Opportunity for Response Assessment at 12 Weeks by Step-up Regimen

	1/20/160 mg (N=20)	0.7/4/20/160 mg (N=40)	Total (N=60)
Study ongoing, n (%)	1 (5.0%)	5 (12.5%)	6 (10.0%)
Off study, n (%)	19 (95.0%)	35 (87.5%)	54 (90.0%)
Study completed, n (%)	1 (5.0%)	0	1 (1.7%)
Study discontinued, n (%)	18 (90.0%)	35 (87.5%)	53 (88.3%)
Primary reason for study discontinuation			
ADVERSE EVENT	0	1 (2.5%)	1 (1.7%)
DEATH	6 (30.0%)	7 (17.5%)	13 (21.7%)
PHYSICIAN DECISION	2 (10.0%)	4 (10.0%)	6 (10.0%)
PROGRESSIVE DISEASE	4 (20.0%)	12 (30.0%)	16 (26.7%)
WITHDRAWAL BY SUBJECT	2 (10.0%)	4 (10.0%)	6 (10.0%)
OTHER	4 (20.0%)	7 (17.5%)	11 (18.3%)

Data cut-off as of Jan 22nd 2024.
Patients who had opportunity for response assessment at 12 weeks exclude patients:
1) who started study drug <77 days prior to data cut off;
2) who started study drug >=77 days and <=91 days prior to cut off, and i) did not die, and ii) did not EOT (due to PD, loss to follow-up, withdrew consent) and EOS, and iii) did not have a tumor assessment within this window.

20 patients received the 1/20 mg regimen, and 40 patients received the 0.7/4/20 mg regimen.

The most common reason for treatment discontinuation was disease progression (33 patients [55.0%]). Seven patients (11.7%) discontinued study drug due to an AE.

Table 41 Selected demographics and baseline characteristics DLBCL with prior CAR-T therapy by updated DCO 22 Jan 2024

Table 14.1.2.1.edtp Demographics and Baseline Characteristics
(Full Analysis Set)
DLBCL Post CAR-T Failure Dose Expansion Patients Who Had Opportunity for Response Assessment at 12 Weeks by Step-up Regimen

	1/20/160 mg (N=20)	0.7/4/20/160 mg (N=40)	Total (N=60)
Age (years)			
n	20	40	60
Mean (SD)	61.5 (13.59)	61.6 (10.47)	61.5 (11.49)
Median	63.0	63.0	63.0
Q1 : Q3	54.0 : 70.5	56.0 : 69.0	55.5 : 69.5
Min : Max	27 : 82	32 : 80	27 : 82
Age Groups (years), n (%)			
< 65	11 (55.0%)	22 (55.0%)	33 (55.0%)
>= 65	9 (45.0%)	18 (45.0%)	27 (45.0%)
Age Groups (years), n (%)			
< 65	11 (55.0%)	22 (55.0%)	33 (55.0%)
>= 65 to < 75	6 (30.0%)	15 (37.5%)	21 (35.0%)
>= 75	3 (15.0%)	3 (7.5%)	6 (10.0%)
Sex, n (%)			
Male	16 (80.0%)	23 (57.5%)	39 (65.0%)
Female	4 (20.0%)	17 (42.5%)	21 (35.0%)

Data cut-off as of Jan 22nd 2024.
Patients who had opportunity for response assessment at 12 weeks exclude patients:
1) who started study drug <77 days prior to data cut off;
2) who started study drug >=77 days and <=91 days prior to cut off, and i) did not die, and ii) did not EOT (due to PD, loss to follow-up, withdrew consent) and EOS, and iii) did not have a tumor assessment within this window.

Table 14.1.2.1.edtp Demographics and Baseline Characteristics
(Full Analysis Set)
DLBCL Post CAR-T Failure Dose Expansion Patients Who Had Opportunity for Response Assessment at 12 Weeks by Step-up Regimen

	1/20/160 mg (N=20)	0.7/4/20/160 mg (N=40)	Total (N=60)
ECOG performance status, n (%)			
0	5 (25.0%)	9 (22.5%)	14 (23.3%)
1	15 (75.0%)	31 (77.5%)	46 (76.7%)
Geographic Region, n (%)			
Europe	5 (25.0%)	7 (17.5%)	12 (20.0%)
North America	15 (75.0%)	29 (72.5%)	44 (73.3%)
Rest of World	0	4 (10.0%)	4 (6.7%)

Data cut-off as of Jan 22nd 2024.

Table 42 Selected tumour characteristics DLBCL with prior CAR-T therapy by updated DCO 22 Jan 2024

Table 14.1.2.2.edtp Baseline Tumor Characteristics
(Full Analysis Set)
DLBCL Post CAR-T Failure Dose Expansion Patients Who Had Opportunity for Response Assessment at 12 Weeks by Step-up Regimen

	1/20/160 mg (N=20)	0.7/4/20/160 mg (N=40)	Total (N=60)
Ann Arbor Stage at Study Entry, n(%)			
I-II	3 (15.0%)	13 (32.5%)	16 (26.7%)
III-IV	17 (85.0%)	27 (67.5%)	44 (73.3%)
Bulky Disease, n(%)			
Yes	10 (50.0%)	14 (35.0%)	24 (40.0%)
No	10 (50.0%)	26 (65.0%)	36 (60.0%)
Histological diagnosis at study entry, n(%)			
Follicular lymphoma Gr 1-3a	0	0	0
Diffuse large B-cell lymphoma	20 (100%)	40 (100%)	60 (100%)
Marginal zone lymphoma	0	0	0
Mantle cell lymphoma	0	0	0
Other B-cell Hodgkin Lymphomas	0	0	0

Data cut-off as of Jan 22nd 2024.
Note: Refractory at the study entry is defined as disease that progressed during previous therapy or relapsed within 6 months from completion of last line of therapy.
Relapse at the study entry is defined as disease that recurred following a response lasting > 6 months from completion of last line of therapy; also include those with unknown/NA best response, however progressed/recurred > 6 months from completion of last line of therapy.
Patients who had opportunity for response assessment at 12 weeks exclude patients:
1) who started study drug <77 days prior to data cut off;
2) who started study drug >=77 days and <=91 days prior to cut off, and i) did not die, and ii) did not EOT (due to PD, loss to follow-up, withdrew consent) and EOS, and iii) did not have a tumor assessment within this window.

Table 14.1.2.2.edtp Baseline Tumor Characteristics
(Full Analysis Set)
DLBCL Post CAR-T Failure Dose Expansion Patients Who Had Opportunity for Response Assessment at 12 Weeks by Step-up Regimen

	1/20/160 mg (N=20)	0.7/4/20/160 mg (N=40)	Total (N=60)
DLBCL cell of origin, n(%)			
GCB (Germinal Center Bcell)	8 (40.0%)	17 (42.5%)	25 (41.7%)
Non-GCB	7 (35.0%)	14 (35.0%)	21 (35.0%)
Unknown	5 (25.0%)	9 (22.5%)	14 (23.3%)
International Prognosis Index for MZL, DLBCL and Other B-NHL, n(%)			
Low (0-1)	4 (20.0%)	5 (12.5%)	9 (15.0%)
Low Intermediate (2)	5 (25.0%)	11 (27.5%)	16 (26.7%)
High Intermediate (3)	6 (30.0%)	13 (32.5%)	19 (31.7%)
High (4-5)	5 (25.0%)	11 (27.5%)	16 (26.7%)

Data cut-off as of Jan 22nd 2024.

The patient population enrolled were pretreated with a median of 3 prior lines of systemic therapies. The majority of patients enrolled in this study had refractory disease, including 76.7% refractory to last line, 78.3% refractory to prior anti-CD20 antibody, and 76.7% refractory to both anti-CD20 antibody and alkylating agent, 71.7% patients were refractory to CAR-T.

Among the 60 patients enrolled in the DLBCL after CAR-T expansion, the median duration of exposure of odronextamab was 12.07 weeks (range 0.7 to 154.1 weeks) and 51.7 of patients had received odronextamab for ≥12 weeks.

The median duration of exposure of odronextamab among DLBCL after CAR-T patients was higher among patients who received the 0.7/4/20 mg step-up regimen compared to 1/20 mg regimen (12.64 weeks vs 5.43 weeks); however, the means were similar (17.65 weeks and 16.87 weeks, respectively), and the range was longer in the 1/20 mg regimen with patients receiving odronextamab for up to 154.1 weeks compared to up to 74.0 weeks in the 0.7/4/20 mg regimen. According to the applicant, this difference is due to enrolment on the 0.7/4/20 mg regimen starting in August 2021 and most of these patients still being on treatment.

Efficacy results

By DCO 22 Jan 2024, the median duration of study follow-up was 16.2 months (95% CI: 8.0 to 17.6 months, n=60); in the 1/20 regimen cohort 9.5 months (95% CI: 2.5 to 30.4 months) vs. the 0.7/4/20 regimen cohort 16.2 months (95% CI: 8.0 to NE months).

Table 43 Primary endpoint - Response rate by IRC in DLBCL with prior CAR-T therapy by updated DCO 22 Jan 2024

Table 14.2.1.1.edtp Summary of Best Overall Response Rate based on Lugano Classification per Independent Central Reviewers
(Full Analysis Set)
DLBCL Post CAR-T Failure Dose Expansion Patients Who Had Opportunity for Response Assessment at 12 Weeks by Step-up Regimen

	1/20/160 mg (N=20)	0.7/4/20/160 mg (N=40)	Total (N=60)
Best Overall Tumor Response, n (%)			
Complete Response (CR)	6 (30.0%)	13 (32.5%)	19 (31.7%)
Partial Response (PR)	2 (10.0%)	8 (20.0%)	10 (16.7%)
Stable Disease (SD)	1 (5.0%)	8 (20.0%)	9 (15.0%)
Progressive Disease (PD)	2 (10.0%)	7 (17.5%)	9 (15.0%)
Not Evaluable (NE)	9 (45.0%)	4 (10.0%)	13 (21.7%)
Response			
Objective Response Rate (ORR:CR+PR)	8 (40.0%)	21 (52.5%)	29 (48.3%)
95% CI for ORR [a]	(19.1%, 63.9%)	(36.1%, 68.5%)	(35.2%, 61.6%)
95% CI for CR Rate [a]	(11.9%, 54.3%)	(18.6%, 49.1%)	(20.3%, 45.0%)
95% CI for PR Rate [a]	(1.2%, 31.7%)	(9.1%, 35.6%)	(8.3%, 28.5%)
Disease Control Rate (DCR: CR/PR/SD)	9 (45.0%)	29 (72.5%)	38 (63.3%)
95% CI for DCR [a]	(23.1%, 68.5%)	(56.1%, 85.4%)	(49.9%, 75.4%)

Data cut-off as of Jan 22nd 2024.
Patients who had opportunity for response assessment at 12 weeks exclude patients:
1) who started study drug <77 days prior to data cut off;
2) who started study drug >=77 days and <=91 days prior to cut off, and i) did not die, and ii) did not EOT (due to PD, loss to follow-up, withdrew consent) and EOS, and iii) did not have a tumor assessment within this window.
[a] Clopper-Person exact confidence interval.

Among DLBCL after CAR-T expansion patients, the ORR per investigator assessment was 41.7% (95% CI: 29.1% to 55.1%). Nineteen patients (31.7%) had CR.

The first response assessment per protocol in study 1333 was performed at week 5 using CT scan. However, the first presented response assessment was from week 12, when a PET-CT was performed. ORR at week 5 per ICR was 23.3% (95% CI: 13.4%, 36.0%) as compared to 48.3% (95% CI: 35.2%, 61.6%) at week 12. Notably, although small sample sizes, the ORR at week 5 was numerically higher (rather than lower) in those treated with the 0.7/4/20 step-up regimen. The ORR at week 5 per ICR was 27.5% (95% CI 14.6%, 43.9%, n=11 of 40) in the 0.7/4/20 step-up cohort vs 15.0% (95% CI 3.2%, 37.9%, n=3 of 20) in the 1/20 step-up cohort.

The overall median duration of follow-up for DOR was 14.8 months (95% CI: 4.3, 16.3 months).

Table 44 DoR in DLBCL with prior CAR-T therapy by updated DCO 22 Jan 2024

Table 14.2.1.4.edtp Kaplan-Meier Estimation of Duration of Response based on Lugano Classification per Independent Central Reviewers
(Full Analysis Set)
DLBCL Post CAR-T Failure Dose Expansion Patients with CR/PR Who Had Opportunity for Response Assessment at 12 Weeks by Step-up Regimen

	1/20/160 mg (N=8)	0.7/4/20/160 mg (N=21)	Total (N=29)
KM Estimation of Duration of Response (CR or PR) (months) [a]			
n	8	21	29
Number of events, n (%)	0	11 (52.4%)	11 (37.9%)
Progressive Disease per Lugano, n (%)	0	8 (38.1%)	8 (27.6%)
Death, n (%)	0	3 (14.3%)	3 (10.3%)
Number of censored patients, n (%)	8 (100%)	10 (47.6%)	18 (62.1%)
Median (95% CI), (months)	NR (NE, NE)	3.3 (2.3, NE)	14.8 (2.8, NE)

Data cut-off as of Jan 22nd 2024.
Patients who had opportunity for response assessment at 12 weeks exclude patients:
1) who started study drug <77 days prior to data cut off;
2) who started study drug >=77 days and <=91 days prior to cut off, and i) did not die, and ii) did not EOT (due to PD, loss to follow-up, withdrew consent) and EOS, and iii) did not have a tumor assessment within this window.
[a] Based on patients with CR or PR.

Table 14.2.1.4.edtp Kaplan-Meier Estimation of Duration of Response based on Lugano Classification per Independent Central Reviewers
(Full Analysis Set)
DLBCL Post CAR-T Failure Dose Expansion Patients with CR/PR Who Had Opportunity for Response Assessment at 12 Weeks by Step-up Regimen

	1/20/160 mg (N=8)	0.7/4/20/160 mg (N=21)	Total (N=29)
Estimated Event-Free Probability , % (95% CI)[a]			
3 months	100 (100, 100)	53.6 (28.2, 73.5)	64.5 (41.2, 80.5)
6 months	100 (100, 100)	47.6 (23.4, 68.5)	59.9 (36.9, 76.8)
9 months	100 (100, 100)	39.7 (16.6, 62.1)	53.2 (29.8, 72.0)
12 months	100 (100, 100)	39.7 (16.6, 62.1)	53.2 (29.8, 72.0)
15 months	100 (100, 100)	31.7 (10.9, 55.2)	46.6 (23.5, 66.8)
18 months	100 (100, 100)	31.7 (10.9, 55.2)	46.6 (23.5, 66.8)
21 months	100 (100, 100)	NE (NE, NE)	46.6 (23.5, 66.8)
24 months	100 (100, 100)	NE (NE, NE)	46.6 (23.5, 66.8)
27 months	100 (100, 100)	NE (NE, NE)	46.6 (23.5, 66.8)
30 months	100 (100, 100)	NE (NE, NE)	46.6 (23.5, 66.8)
33 months	100 (100, 100)	NE (NE, NE)	46.6 (23.5, 66.8)
36 months	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)

Data cut-off as of Jan 22nd 2024.

Table 45 DoCR in DLBCL with prior CAR-T therapy by updated DCO 22 Jan 2024

Table 14.2.1.5.edtp Kaplan-Meier Estimation of Duration of Response in Patients with Best Overall Response CR based on Lugano Classification per Independent Central Reviewers (Full Analysis Set)
DLBCL Post CAR-T Failure Dose Expansion Patients with Best Overall Response CR Who Had Opportunity for Response Assessment at 12 Weeks by Step-up Regimen

	1/20/160 mg (N=6)	0.7/4/20/160 mg (N=13)	Total (N=19)
KM Estimation of Duration of Response (CR or PR) (months) [a]			
n	6	13	19
Number of events, n (%)	0	4 (30.8%)	4 (21.1%)
Progressive Disease per Lugano, n (%)	0	3 (23.1%)	3 (15.8%)
Death, n (%)	0	1 (7.7%)	1 (5.3%)
Number of censored patients, n (%)	6 (100%)	9 (69.2%)	15 (78.9%)
Median (95% CI), (months)	NR (NE, NE)	NR (2.3, NE)	NR (3.3, NE)

Data cut-off as of Jan 22nd 2024.
Patients who had opportunity for response assessment at 12 weeks exclude patients:
1) who started study drug <77 days prior to data cut off;
2) who started study drug >=77 days and <=91 days prior to cut off, and i) did not die, and ii) did not EOT (due to PD, loss to follow-up, withdrew consent) and EOS, and iii) did not have a tumor assessment within this window.
[a] Based on patients with CR.

Table 14.2.1.5.edtp Kaplan-Meier Estimation of Duration of Response in Patients with Best Overall Response CR based on Lugano Classification per Independent Central Reviewers (Full Analysis Set)
DLBCL Post CAR-T Failure Dose Expansion Patients with Best Overall Response CR Who Had Opportunity for Response Assessment at 12 Weeks by Step-up Regimen

	1/20/160 mg (N=6)	0.7/4/20/160 mg (N=13)	Total (N=19)
Estimated Event-Free Probability , % (95% CI)[a]			
3 months	100 (100, 100)	80.0 (40.9, 94.6)	85.7 (53.9, 96.2)
6 months	100 (100, 100)	70.0 (32.9, 89.2)	78.6 (47.2, 92.5)
9 months	100 (100, 100)	70.0 (32.9, 89.2)	78.6 (47.2, 92.5)
12 months	100 (100, 100)	70.0 (32.9, 89.2)	78.6 (47.2, 92.5)
15 months	100 (100, 100)	56.0 (19.7, 81.3)	68.8 (35.7, 87.3)
18 months	100 (100, 100)	56.0 (19.7, 81.3)	68.8 (35.7, 87.3)
21 months	100 (100, 100)	NE (NE, NE)	68.8 (35.7, 87.3)
24 months	100 (100, 100)	NE (NE, NE)	68.8 (35.7, 87.3)
27 months	100 (100, 100)	NE (NE, NE)	68.8 (35.7, 87.3)
30 months	100 (100, 100)	NE (NE, NE)	68.8 (35.7, 87.3)
33 months	100 (100, 100)	NE (NE, NE)	68.8 (35.7, 87.3)
36 months	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)

Data cut-off as of Jan 22nd 2024.

Three patients were eligible for transition from Q2W to Q4W and all 3 transitioned to Q4W dosing. At the time of DCO 22 Jan 2024, 1 patient had ongoing treatment and 2 patients were in follow-up. None of these patients progressed after transition.

Table 46 Time to response in DLBCL with prior CAR-T therapy by updated DCO 22.01.2024

Table 14.2.1.28.edtp Observed Time to Response based on Lugano Classification per Independent Central Reviewers
(Full Analysis Set)
DLBCL Post CAR-T Failure Dose Expansion Patients with CR/PR Who Had Opportunity for Response Assessment at 12 Weeks by Step-up Regimen

	1/20/160 mg (N=8)	0.7/4/20/160 mg (N=21)	Total (N=29)
Observed Time to Response (CR or PR) (months) [a]			
n	8	21	29
Mean (SD)	2.04 (0.856)	1.90 (1.114)	1.94 (1.036)
Median	2.56	1.38	1.84
Q1 : Q3	1.10 : 2.68	1.02 : 2.56	1.02 : 2.60
Min : Max	0.9 : 2.8	0.9 : 5.4	0.9 : 5.4
Observed Time to Response (CR or PR), n (%) [a]			
<6 weeks	3 (37.5%)	10 (47.6%)	13 (44.8%)
>=6 weeks and < 3 months	5 (62.5%)	9 (42.9%)	14 (48.3%)
>=3 months and <6 months	0	2 (9.5%)	2 (6.9%)
>=6 months	0	0	0

Data cut-off as of Jan 22nd 2024.
Patients who had opportunity for response assessment at 12 weeks exclude patients:
1) who started study drug <77 days prior to data cut off;
2) who started study drug >=77 days and <=91 days prior to cut off, and i) did not die, and ii) did not EOT (due to PD, loss to follow-up, withdrew consent) and EOS, and iii) did not have a tumor assessment within this window.
[a] Based on patients with CR or PR.

Table 47 Time to complete response in DLBCL with prior CAR-T therapy by updated DCO 22.01.24

Table 14.2.1.32.edtp Observed Time to Complete Response based on Lugano Classification per Independent Central Reviewers
(Full Analysis Set)
DLBCL Post CAR-T Failure Dose Expansion Patients with CR Who Had Opportunity for Response Assessment at 12 Weeks by Step-up Regimen

	1/20/160 mg (N=6)	0.7/4/20/160 mg (N=13)	Total (N=19)
Observed Time to Complete Response (CR) (months) [a]			
n	6	13	19
Mean (SD)	2.88 (1.358)	3.30 (1.260)	3.17 (1.269)
Median	2.66	2.83	2.76
Q1 : Q3	2.56 : 2.86	2.60 : 3.45	2.56 : 3.45
Min : Max	1.2 : 5.4	1.8 : 5.6	1.2 : 5.6
Observed Time to Complete Response (CR), n (%) [a]			
< 6 weeks	1 (16.7%)	0	1 (5.3%)
>=6 weeks and < 3 months	4 (66.7%)	9 (69.2%)	13 (68.4%)
>=3 months and <6 months	1 (16.7%)	4 (30.8%)	5 (26.3%)
>=6 months and <9 months	0	0	0
>=9 months	0	0	0

Data cut-off as of Jan 22nd 2024.
Patients who had opportunity for response assessment at 12 weeks exclude patients:
1) who started study drug <77 days prior to data cut off;
2) who started study drug >=77 days and <=91 days prior to cut off, and i) did not die, and ii) did not EOT (due to PD, loss to follow-up, withdrew consent) and EOS, and iii) did not have a tumor assessment within this window.
[a] Based on patients with CR.

The first response assessment per protocol was at week 5 using CT scan; however, the first response assessment that included PET-CT was at week 12. The majority of responses (93.1%) were evident by the time of response assessment at 12 weeks.

Table 48 PFS in DLBCL with prior CAR-T therapy by updated DCO 22 Jan 2024 per Independent review

(Full Analysis Set)
DLBCL Post CAR-T Failure Dose Expansion Patients Who Had Opportunity for Response Assessment at 12 Weeks by Step-up Regimen

	1/20/160 mg (N=20)	0.7/4/20/160 mg (N=40)	Total (N=60)
Number of events, n (%)	11 (55.0%)	29 (72.5%)	40 (66.7%)
Progressive Disease per Lugano, n (%)	3 (15.0%)	18 (45.0%)	21 (35.0%)
Death, n (%)	8 (40.0%)	11 (27.5%)	19 (31.7%)
Number of censored patients, n (%)	9 (45.0%)	11 (27.5%)	20 (33.3%)
Median (95% CI), (months)[a]	2.7 (1.0, NE)	4.8 (2.6, 6.2)	4.8 (2.6, 5.4)

Data cut-off as of Jan 22nd 2024.
Patients who had opportunity for response assessment at 12 weeks exclude patients:
1) who started study drug <77 days prior to data cut off;
2) who started study drug >=77 days and <=91 days prior to cut off, and i) did not die, and ii) did not EOT (due to PD, loss to follow-up, withdrew consent) and EOS, and iii) did not have a tumor assessment within this window.
[a] Based on Kaplan-Meier method.

Table 49 OS in DLBCL with prior CAR-T therapy by updated DCO 22 Jan 2024

Table 14.2.2.1.edtp Overall Survival
(Full Analysis Set)
DLBCL Post CAR-T Failure Dose Expansion Patients Who Had Opportunity for Response Assessment at 12 Weeks by Step-up Regimen

	1/20/160 mg (N=20)	0.7/4/20/160 mg (N=40)	Total (N=60)
Number of deaths, n (%)	10 (50.0%)	24 (60.0%)	34 (56.7%)
Number of censored patients, n (%)	10 (50.0%)	16 (40.0%)	26 (43.3%)
Median (95% CI), (months)[a]	3.7 (1.1, NE)	10.5 (5.4, 15.8)	10.2 (4.6, 15.8)

Data cut-off as of Jan 22nd 2024.
Patients who had opportunity for response assessment at 12 weeks exclude patients:
1) who started study drug <77 days prior to data cut off;
2) who started study drug >=77 days and <=91 days prior to cut off, and i) did not die, and ii) did not EOT (due to PD, loss to follow-up, withdrew consent) and EOS, and iii) did not have a tumor assessment within this window.
[a] Based on Kaplan-Meier method.

Overall, the Applicant provided data from the "DLBCL after CAR-T expansion" cohort of the supportive study 1333, with completed target enrollment of 60 patients. ORR was 48.3% (95% CI 35.2% to 61.6%) and CR of 31.7% (95% CI 20.3% to 45.0%) as assessed by ICR. The KM estimated median duration of response (CR/PR) was 14.8 months (95% CI 2.8, NE), median duration of CR was not reached (95% CI 3.3, NE) months.

2.6.5.6.2. Real world data

Historical control data has been requested in given advice for contextualization and these data are therefore appreciated.

Retrospective observational studies

- The applicant has performed 2 **retrospective observational studies** evaluating real world treatment in patients with r/r FL (R1979-ONC-20103 [FLORA]) and r/r DLBCL (R1979-ONC-2090 [ORCHID]) initiating systemic treatment after at least 2 prior lines of therapy in North America, Europe, and Asia. At the time of pre-submission meeting with the Rapporteurs in May 2023, the applicant stated that all clinical data has been obtained and that abbreviated study reports for both studies will be provided as a part of the responses to Day 120 LoQ, and the full reports will be available at the time of the response to Day 180 LoOI.

The ORCHID study included real-world patients (i.e., patients outside studies) who initiated 3rd line and above (3L+) treatments from 01 Jan 2015 to 30 Jun 2021 (allowing up to 6 months of potential follow-up).

The FLORA study included real-world patients who initiated 3L+ treatments from 01 Jan 2015 to 31 Dec 2020 (allowing up to 12 months of potential follow-up).

Data were collected retrospectively from a combination of electronic medical record (EMR) or research database extraction of structured data and manual abstraction of unstructured records from 26 oncology centres in Asia, Europe, and North America.

A total of 138 patients who contributed 148 index line of therapies were included in the ORCHID cohort following IPTW with each patient contributing up to 3 lines of therapy.

Similarly in the FLORA study, the primary analysis was performed based on a total of 83 patients who contributed 100 LOTs following IPTW, with each patient contributing up to 3 lines of therapy.

The primary endpoint was ORR assessed by ICR of scans based on Lugano criteria of response.

Importantly, the selection process for patients in the odronextamab trials and the retrospective chart reviews differ, as do the times during which they were recruited, which includes the introduction of CAR-T cells as an option, as well as the Covid-19 pandemic.

The impact of the selection process in terms of potential bias probably cannot be fully understood. Moreover, the impact of loss to follow up in ORCHID and FLORA, is not fully understood by the assessor.

The applicant notes that patients in ORCHID and FLORA tended to have less severe disease before IPTW-weighting, any residual bias not addressed by IPTW is expected to result in better outcomes in the real-world patients thereby making the contextualization conservative.

Furthermore, given the lack of a protocol-defined schedule of assessments, the frequency and timing of assessments differed in Study 1625 vs. the real-world, thus complicating the reliable estimation of time to event endpoints.

The primary outcome was ORR. Results show higher ORR and CR with odronextamab than in the retrospectively matched cohort for both DLBCL and FL. Comparing DoR and PFS is fraught with large uncertainty due to different and varying assessment schedules in the matched control group.

OS estimates indicate better survival in patients with FL treated with odronextamab compared to the FLORA control. With regards to OS in DLBCL, the outcome in odronextamab treated patients is roughly similar to the overall population in ORCHID.

Patients in the control group that underwent leukapheresis for CAR-T treatment had longer survival than those treated with odronextamab in the 1625 study, whereas the opposite was the case for those not intended for car-t treatment.

Conclusion on the Retrospective observational studies

In summary, the applicant has provided contextualisation of the findings in the single arm trial experience. These describe a higher ORR, and no signal of harm with respect to OS.

Several limitations in the estimation of study endpoints are recognized, for instance differential selection processes for the groups compared, possible incompleteness of information captured in the medical records, differences in the frequency and timing of scan assessment, heterogeneity in patient care across countries, changing treatment landscape, the covid pandemic, not all countries represented.

For the same methodological reasons that patients selected through a retrospective chart review could not be used to establish the efficacy of odronextamab or similar products, no inferences on efficacy are drawn.

Systematic literature review

- The applicant has also conducted a protocol-driven **systematic literature review** of 3L+ systemic treatments in r/r FL and r/r DLBCL.

With regard to the systematic literature review, the applicant has clearly addressed the well-known limitations of such data due to large differences in populations and considerable heterogeneity in several other crucial parameters that hampers any form of meaningful comparison.

2.6.5.6.3. Proposed confirmatory trials for the purpose of the CMA

The Applicant proposes the below study to be considered Specific Obligations of the CMA.

Follicular lymphoma

Study R1979-ONC-22102 is a Phase 3, open label, randomized study to compare the efficacy and safety of odronextamab in combination with lenalidomide therapy versus rituximab in combination with lenalidomide (R2) therapy in participants with R/R FL and MZL in > 2 line.

The analysis of odronextamab efficacy in study R1979-ONC-22102 will be tested in the FL population and in the overall indolent NHL population, which includes FL and MZL. The Applicant states that the study is adequately powered to demonstrate efficacy in FL patients. This is considered appropriate.

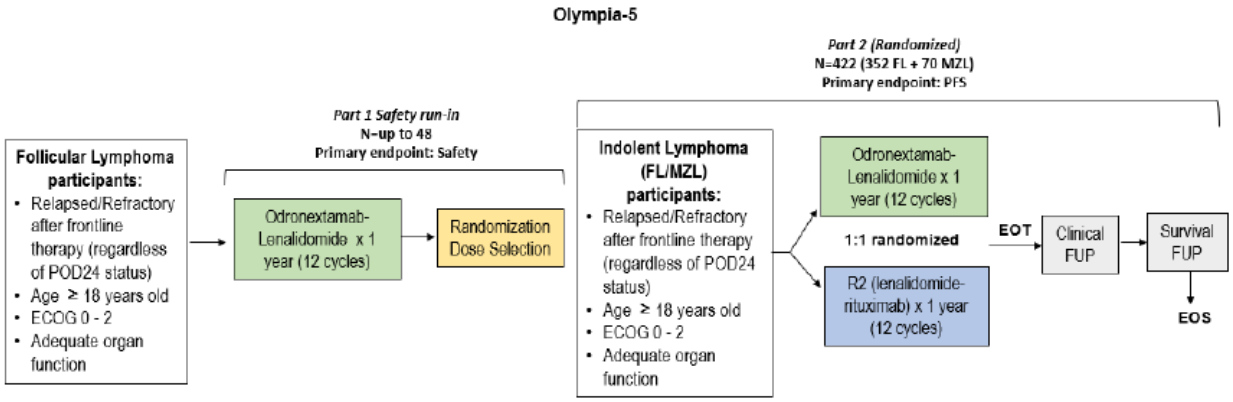
Preliminary results from studies with other anti-CD20x anti-CD3 bispecific antibodies (such as mosunetuzumab and epcoritamab) in combination with lenalidomide have shown that the safety was manageable together with encouraging anti-lymphoma activity in patients with indolent lymphoma (Leonard, 2022). According to the applicant, it may be anticipated that the safety of odronextamab in combination with lenalidomide in patients with R/R indolent lymphoma will be manageable.

Lenalidomide (12 cycles) given in combination with rituximab during cycles 1 to 5 is widely accepted as standard therapy in indolent lymphoma and was approved by multiple health authorities (NCCN 2022, Dreyling 2021) and serve as the active comparators for this study.

Approximately 420 participants will be enrolled and will be randomly assigned in a 1:1 ratio to receive either (A) odronextamab in combination with lenalidomide, or (B) rituximab in combination with lenalidomide (R2) for up to 12 cycles of therapy.

The study will be conducted globally in North America, Europe, Asia Pacific, Latin America in at least 18 countries and approximately 200 sites. Enrollment has started and information on the progress has been provided to the EMA.

Figure 17 Olympia-5 Study R1979-ONC-22102 schema



Note: Enrolment of participants with MZL will begin following clearance of safety in the first 25 participants treated with the 0.7/4/20 mg step-up regimen in the MZL cohort in the ongoing phase 2 study (R1979-ONC-1625).

The primary endpoint of PFS is assessed by IRC.

The projected final CSR will be provided by September 2031.

DLBCL

Study R1979-HM-2299 is a Phase 3, randomized, open label study, evaluating efficacy and safety of odronextamab versus Standard of Care (SOC) salvage therapy followed by ASCT in participants with R/R aggressive B-cell non-Hodgkin lymphoma.

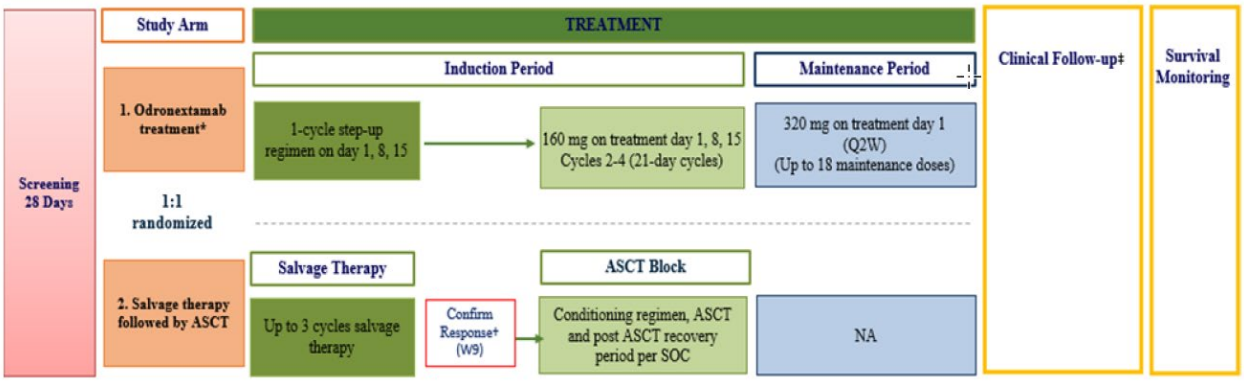
Participants will be randomized 1:1 to receive either odronextamab or SOC. In total, 216 patients will be enrolled in this study.

The primary objective is EFS, in participants with odronextamab versus participants with SOC. While EFS including new anti-lymphoma therapy as an event, has been accepted previously in the present setting, a positive study driven by such events, and without a positive secondary PFS analysis, may be considered not to have established the efficacy of Ordspono. However, given the inclusion of non-progression elements in the EFS-definition, benefit should be corroborated by the PFS outcome.

Notably, the Applicant informs that the timing of response assessments between the odronextamab arm (arm 1) and the standard of care arm (arm 2) in study 2299 will be aligned, to avoid any potential bias in the EFS and PFS analyses. Thus, the first response assessment in both arms will be performed at week 9 (±1 week). This resolves a concern raised on assessment of the study proposal. PFS is a key secondary endpoint for Study 2299. Per the hierarchical testing procedure for primary endpoint and secondary endpoints described in the protocol, PFS will be the first key secondary endpoint to be tested if EFS is statistically significant.

OS is defined as an Additional secondary endpoint in the protocol of study 2299

Figure 18 OLYMPIA-4 Study R1979-HM-2299 schema



The study is being conducted globally in Europe, Asia Pacific, and Latin America. Enrollment has started and information on the progress has been provided tpo the EMA.

The Applicant estimates that the CSR will be submitted by November 2028.

Residual uncertainty about the impact of treatment on OS is intrinsic to the single arm design of the pivotal study. This highlights the importance of delivering interpretable OS data in the confirmatory studies related to a CMA for both FL and DLBCL. Protocol specified cross-over options after progression in the control arm should be avoided, to provide comprehensive data including interpretable estimates of the impact of the product on OS, in the context of a CMA. Experience shows that cross-over substantially hampers the interpretation of OS data. Thus, in order to provide comprehensive data on odronextamab, the applicant has agreed to remove the cross-over option from the confirmatory trial R1979-HM-2299 in DLBCL. The protocol will be amended.

2.6.6. Discussion on clinical efficacy

Design and conduct of clinical studies

To support the proposed indications in in r/r FL and r/r DLBCL, the applicant submitted data from the pivotal phase 2 study 1625 and from the supportive phase 1 study 1333 which included a cohort for patients with DLBCL who had progressed after CAR-T therapy.

Pivotal Study 1625 FL and DLBCL

The pivotal study 1625 is an ongoing open-label, single-arm, multi-center, phase 2 study of odronextamab in patients with 5 disease-specific B-NHL cohorts: FL, DLBCL, MCL, MZL, and other B-NHL that have relapsed after or are refractory to prior systemic therapy.

According to the inclusion criteria, patients should, in the judgment of the investigator, require systemic therapy for lymphoma at the time of study enrollment. Patient with prior CAR-T therapy, prior allogeneic stem cell transplantation, or CNS involvement of lymphoma were excluded. Confirmed CD20 positivity at enrollment was not an inclusion criterion, despite the mechanism of action with a bispecific CD20/CD3 antibody as odronextamab. Overall, the study entry criteria define FL and DLBCL populations appropriate for the proposed treatment and reflect the sought target populations of FL and DLBCL.

According to the inclusion criteria, DLBCL NOS - GCB type/ABC type were the eligible subtypes (WHO 2017) in study 1625. However, the enrolment in the DLBCL cohort was based on local pathology assessments by site investigators, and the information on MYC, BCL2, and BCL6 rearrangements was sometimes unknown at the time of enrolment. Frequent changes in the nomenclature and classification

of DLBCL led the investigators to use the term "DLBCL" as the diagnosis in the absence of fluorescence in situ hybridisation testing. Therefore, some patients in the DLBCL cohort were identified with gene rearrangements (and by that HGBL diagnosis) after enrolment. Based on the updated data from 20 October 2023 DCO, the number of HGBL patients in DLBCL 160 mg cohort is 11 (8.7%).

The subtype "Transformations of indolent B-cell lymphomas" has recently been implemented in the 5th WHO classification of 2022 (under the category Mature B-cells neoplasms) but has previously not been specified in the WHO classification. In SmPC section 5.1, the applicant has specified that lymphoma classification in study 1625 was based on WHO classification 2017, i.e., the revised 4th edition, for both FL and DLBCL.

Selected RP2D regimens were: 80 mg QW/160 mg Q2W followed by 160 mg Q4W for FL; 160 mg QW/320 mg Q2W followed by 320 mg Q4W for DLBCL. Odronextamab was administered IV, first in 4 cycles (each cycle was 21-day) and then in a maintenance phase with Q2W dosing. If a patient had maintained CR for 9 months, then odronextamab was to be administered every 4 weeks at the same dose.

From the accumulated data obtained with the initially used 1/20 mg step-up regimen from both studies 1625 and 1333, a rate of 9% grade ≥3 CRS was observed in all B-NHL patients. At this point, there was a pause in enrollment in both studies, due to a partial clinical hold imposed by the FDA, during which the sponsor revised the step-up dosing regimen to mitigate the risk of CRS. Based on the totality of information (clinical CRS data, odronextamab concentrations, IL-6 concentrations, and the QSP model-based assessment), the 0.7/4/20 mg regimen was then implemented in Study 1625 and Study 1333 in conjunction with the enhanced premedication, intensified monitoring during step-up dosing, and earlier interventions with tocilizumab and higher corticosteroid doses. The proposed premedication in SmPC section 4.2 is considered appropriate and in line with the premedication from protocol amendment 5.

The primary endpoint was ORR according to the Lugano Classification of response in malignant lymphoma (Cheson, 2014) and as assessed by independent central review for each of the five disease-specific cohorts in study 1625. Secondary endpoints included CR, DoR, PFS, and OS. Overall, the objectives and endpoints are considered appropriate for a phase 2 single-arm trial, and of clinical relevance.

In global amendment 2, inclusion criterion for FL was upgraded to require patients to have failed combination lenalidomide and rituximab treatment, where approved, or have been deemed not appropriate to receive this treatment. However, prior treatment with lenalidomide in combination with rituximab was not applicable for majority of patients in study 1625 due to rituximab refractoriness and the fact that this combination was not approved or available in several countries where study 1625 was conducted. Thirteen percent of the FL patients had received prior lenalidomide in combination with rituximab.

The original SAP is dated 17 December 2021 and was based on the global protocol amendment 4, prior to database lock 23 March 2023, and prior to the administrative review which was added with amendment 5 in April 2022. First patient first dose FL on 0.7/4/20 regimen was 06 Sep 2021. First patient first dose DLBCL on 0.7/4/20 regimen was 18 Aug 2021. Thus, the SAP was written about 3 months after start of inclusion of patients with the revised step-up regimen. Overall, the reported protocol deviations in study 1625 are not considered to impact the overall efficacy conclusions in the FL or DLBCL cohort.

Study 1625 provides efficacy data from the interim efficacy analysis in patients with FL, and from the primary efficacy analysis in patients with DLBCL. The full analysis set (FAS) included all enrolled

patients who received any dose of odronextamab. Efficacy Analysis Set included all enrolled patients who received any dose of odronextamab and had the opportunity for efficacy assessment at 12 weeks.

The FAS (n=281) in study 1625 included the both the global cohort (n=255) and the Japan and China country-specific extension cohorts (n=26). The purpose of the country specific cohorts (Study 1625 Global Protocol Amendment 5) was to fulfill regulatory requirements in Japan and China, but they were not included in the primary efficacy analysis.

The primary efficacy analysis was limited to the global cohort where 128 FL 80 mg patients and 127 DLBCL 160 mg patients had the opportunity to have the 12-week assessment (Efficacy analysis set, which is also the FAS of the global cohort). Thus, the efficacy analyses in SmPC section 5.1 are based on the FAS from the global cohort.

Sample size for each cohort is calculated based on the binomial distribution and a lower bound of the 95% CI that is expected to be above the cohort-specific minimal clinically meaningful ORR. No formal statistical testing was planned for this study due to no comparator arm in the study. However, sample size for each cohort was calculated with the expectation to observe an ORR with 95% CI above the cohort-specific minimal clinically meaningful ORR. This corresponds to a statistical testing against a pre-specified value. All analyses were descriptive in nature and were summarized by disease-specific cohort.

The primary efficacy endpoint was Objective response rate (ORR). Estimates of response rate, along with its exact two-sided 95% CI by Clopper and Pearson were presented. ORR is derived using the number of subjects, why sample size of the analysis population is of particular importance for the ORR estimate.

The protocol and the SAP stipulated that efficacy would be analysed using FAS. FAS was in the protocol defined to include all patients who received any study drug, while according to the SAP, the FAS included all enrolled patients who receive any doses of odronextamab. The definition of FAS is acceptable.

The interim report summarizes the ORR per dosing regimen (i.e., 1/20 regimen, and the modified 0.7/4/20 regimen). Analysis set for neither of dosing regimens fulfils the planned criterion for interim analysis in respect to the number of subjects or duration of follow-up. As can be recalled, the pre-specified interim efficacy analysis for primary efficacy endpoint was planned to be performed when 80 patients with FL grade 1-3a have completed 52-week assessment and all patients in the DLBCL cohort have completed 36-week assessment or have withdrawn from the study, whichever is later.

The SAP was based on the protocol amendment 4 which incorporated numerous changes in the study design concerning the number and selection criteria for the included cohorts, treatment duration, treatment dosing regimen, sample size, plans for interim analyses, etc. There were numerous changes to the statistical analysis plan in this open label study. Considering the statistical issues, the study 1625 was regarded as an explorative with no control of type I error.

Supportive Study 1333 - DLBCL after CAR-T therapy

Study 1333 is a first-in-human, phase 1, open-label, multicenter, dose-finding and expansion study of odronextamab monotherapy in patients with CD20+ B-cell malignancies previously treated with anti-CD20 antibody therapy. The study consisted of a dose escalation portion followed by disease-specific expansions.

The key entry criteria for the disease-specific expansion cohort enrolling "DLBCL patients after CAR-T therapy", was that the patient should have recovered from the toxicities of the lymphodepletion therapy and CAR-T infusion. As with Study 1625, patients were not tested for CD20 expression for study entry.

In the dose escalation phase and 17 dose levels were tested, which included 13 different step-up increments tested at weeks 1 and 2. There was a pause in enrolment in both study 1625 and 1333, due to a partial clinical hold imposed by the FDA on 11 Dec 2020 due to the incidence of grade ≥3 CRS events in patients treated with 1/20 mg step-up regimen which resulted in the revised 0.7/4/20 mg a step-up regimen.

The primary endpoints included safety and also ORR for the post CAR-T expansion cohort according to the Lugano Classification (Cheson, 2014) by independent central review. In study 1333, there was no formal hypothesis test, and all the analyses were descriptive in nature.

The Applicant provided data from the DLBCL after CAR-T cohort from Study 1333 with completed target enrolment of 60 patients from the primary analysis, DCO 22 Jan 2024. The median duration of study follow-up was 16.2 months (95% CI: 8.0 to 17.6 months). The FAS included all patients enrolled in the DLBCL after CAR-T cohort. The Efficacy Analysis Set in the "DLBCL After CAR-T Expansion Cohort" enrolled patients who received any dose of odronextamab and had the opportunity for efficacy assessment at 12 weeks.

Efficacy data and additional analyses

Pivotal Study 1625 FL and DLBCL

Efficacy data for FL

As of data cutoff date of 31 Jan 2023, 128 patients with FL were efficacy evaluable (defined as patients with or who had the opportunity for response assessment at 12 weeks); 60 patients received the 0.7/4/20 regimen, 68 patients received the 1/20 regimen.

The baseline data reflect a r/r FL population after multiple systemic therapies, which is in line with the sought indication. Overall, the median (range) age was 61.0 (22 to 84) years, and the median (range) number of prior lines was 3 (2 to 13). It is noted that at high proportion of the patients (46%) were refractory to first line treatment.

As of updated DCO 20 Oct 2023, ORR (primary endpoint, n=128) was 80.5% (95% CI: 72.5%, 86.9%), with a CR in 73.4% (95% CI: 64.9%, 80.9%) of the patients. This is considered to be clinically relevant in patients with r/r FL after 2 prior lines of therapy.

The lower bound of the 95% CI for ORR exceeded the 49% rate prespecified ORR in the SAP, which was chosen by the applicant as the minimum clinically meaningful ORR for the FL cohort.

Despite the single-arm study design and limited sample size, activity of odronextamab is evident and can be isolated. Spontaneous remissions are not expected in r/r FL after 2 prior lines in patients for whom systemic therapy is indicated.

According to the subgroup analysis, the ORR results are not considered to be driven by a specific subgroup. However, numerically lower ORR rates are noted in older patients > 75 years and in patients with bulky disease, which may be expected.

Time to response and Time to complete response were similar between the two different step-up regimens. However, the first response assessment per protocol was at week 12, therefore quantification of time to response before that time is not possible. Most responses (88.3%) were evident by the time of first response assessment. The median observed TTR was 2.7 months (range: 1.8 to 7.9). Further, most CRs (85.1%) patients) were evident by the time of first response assessment, and median observed TTCR was 2.7 months (range 2.3 to 7.9).

PFS and OS (secondary endpoints) are time dependent endpoints that do not isolate drug effects in a single-arm trial.

The Applicant provided top line efficacy data from the other cohorts (ie, FL grade 3b, MCL, MZL. Other B-NHL) from Study 1625 based on Oct 2023 data cutoff. Responses were noted across all subtypes. Moreover, throughout Study 1625, 2 pre-specified interim and the primary analysis for FL and 1 pre-specified interim and the primary analysis for DLBCL were conducted. The efficacy results are consistent over time in both FL and DLBCL cohorts.

Efficacy data for DLBCL

As of data cutoff date of 31 Jan 2023, 127 patients with R/R DLBCL treated with 160 mg in study 1625 were efficacy evaluable (defined as patients with or who had opportunity for response assessment at 12 weeks); 67 patients received the 1/20 mg regimen, and 60 patients received the 0.7/4/20 mg regimen.

The baseline data reflect a r/r DLBCL population after multiple systemic therapies, which is in line with the sought indication. Overall, the median (range) age was 67.0 (24 to 88) years, and the median (range) number of prior lines was 2 (2 to 8). The minor numerically differences in baseline characteristics between the 2 step-up regimens are not considered to have a substantial impact on the efficacy results for DLBCL.

As of updated DCO 20 Oct 2023, ORR (primary endpoint, n=127) was 52% (95% CI 43, 61), with a CR rate in 32% (95% CI 24, 40) of the patients. This is considered clinically relevant in patients with r/r DLBCL after 2 prior lines of therapy.

The lower bound of the 95% CI for ORR exceeded the 35% rate prespecified ORR in the SAP, which was chosen by the applicant as the minimum clinically meaningful ORR for the DLBCL cohort.

Despite the single-arm study design and limited sample size, the activity of odronextamab is evident and can be isolated. Spontaneous remissions are not expected in r/r DLBCL after 2 prior lines of therapy.

According to the subgroup analysis, the ORR results are not considered to be driven by a specific subgroup. However, numerically lower ORR rates are noted in patients with bulky disease and double/triple-hit lymphoma, which may be expected.

It is noted an ORR of 79% in patients not prior refractory to anti-CD20 antibody vs 44% ORR in patients that were prior refractory to anti-CD20 antibody. Notwithstanding the well-known limitations of subgroup analyses, these findings highlight the need for the applicant to present efficacy data in patients with CD20 positive vs negative disease.

Time to response and Time to complete response were similar between the two different step-up regimens, which points towards homogeneity in response. However, the first response assessment per protocol was at week 12, therefore quantification of time to response before that time is not possible. Most responses (86.4%) were evident by the time of first response assessment. The median observed TTR was 2.6 months (range: 0.8 to 6.4). Further, most CRs (72.5%) were evident by the time of first response assessment, and median observed TTCR was 2.6 months (range 1.4 to 8.1).

PFS and OS (secondary endpoints) are time dependent endpoints that do not isolate drug effects in a single-arm trial.

The agreed indication is: *"Ordspono as monotherapy is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (r/r DLBCL) after two or more lines of systemic therapy."*

Supportive Study 1333 - DLBCL after CAR-T therapy

Overall, the Applicant provided data from the "DLBCL after CAR-T expansion" cohort of the supportive study 1333, with completed target enrollment of 60 patients. According to the latest data update (22 Jan 2024, primary analysis, n=60), ORR was 48.3% (95% CI 35.2% to 61.6%) and CR of 31.7% (95% CI 20.3% to 45.0%) as assessed by ICR. The KM estimated mDoR was 14.8 months (95% CI 2.8, NE), median duration of CR was not reached (95% CI 3.3 NE) months. This is sufficient for inclusion in the SmPC section 5.1.

Proposed dosing regimens; study 1625 FL and DLBCL

Homogeneity of response between the two step-up regimens

For both FL and DLBCL, the applicant argues that there is homogeneity in response between the 1/20 and 0.7/4/20 mg step-up regimens that justifies the proposed pooling of efficacy data. It is agreed that there is a biological rationale for expecting a homogeneous response in both FL and DLBCL regardless of step-up regimen, since the difference between the two regimens is limited in terms of drug exposure. The selected and adapted 0.7/4/20 mg step-up regimen merely entails the addition of 1 extra week before reaching the first full dos of odronextamab. Thus, it does not seem reasonable to believe that there would be a difference in efficacy.

Considering the limited sample sizes and the so far short follow-up duration in the 0.7/4/20 mg step-up cohorts, it is not possible to positively demonstrate homogeneity in efficacy estimates. Available data, however, are compatible with the homogeneity assumption. Obviously, the study was not designed to demonstrate homogeneity, and this is not needed as it is not questioned. This entails that results from the 1/20 mg step-up cohorts are relevant also for the 0.7/4/20 mg step-up cohorts. Thus, the pooling of efficacy data from the different step-up regimens is accepted.

By the updated DCO (20 Oct 2023), the median duration of study follow-up was 20.1 months (95% CI 17.3 to 27.8 months) for the **FL cohort** (n=128). The median estimated duration of follow-up was 15.9 months (95% CI 14.7-17.2) for the 0.7/4/20 regimen vs 34.2 months (95% CI 33.2-35.7) for the 1/20 regimen.

The updated mDoR for patients with FL (n=128) was 22.6 months (17.7 to NE). This is considered clinically meaningful and similar to the response duration reported from bispecific antibody mosunetuzumab for the same condition. The mDoR was still not reached (95% CI: 17.0, NR, n=46) for FL patients who received the 0.7/4/20 regimen vs. a mDoR of 20.5 months (95% CI: 14.8, 32.2, n=57) for patients who received the 1/20 regimen.

The updated median duration of study follow-up was 32.5 months (95% CI 17.4 to 36.3 months) for the **DLBCL cohort** (n=127). The median estimated duration of follow-up was 17.3 months (95% CI 12.4-23.0) for the 0.7/4/20 mg regimen vs 36.3 months (95% CI 32.5-38.8) for the 1/20 mg regimen.

The updated median DoR for patients with **DLBCL** (n=127) was 10.5 months (95% CI 5.0 to 24.8). This is considered clinically meaningful. Moreover, the median is within the 95% CI of the medians for other bispecific antibodies for the same condition.

The median DoR was 8.6 months (95% CI: 3.3 to 13.9 months, n=31) for DLBCL patients who received 0.7/4/20 regimen vs a mDoR of 17.9 months (95% CI:5.4, NE, n=35) for patients who received the 1/20 regimen. Thus, a numerically shorter mDoR is observed for DLBCL patients who received the 0.7/4/20 regimen in the updated efficacy analyses, vs the 1/20 regimen cohort.

Response duration depends both on drug activity and intrinsic tumour growth kinetics. Therefore, this does not isolate drug effects in a strict sense. Moreover, the DoR dataset is defined by a post-baseline event (objective response) and needs to be interpreted with caution in a single-arm trial. Also,

comparison between dosing regimens is not randomized. Finally, the CHMP has concluded that there is little biological rationale to support a true difference in durability of response due to the changed step up regimen. It suffices to say that the overall DoR is clinically meaningful by commonly applied standards, and thus similar to those of other products in class.

Proposed posology with transition from Q2W to Q4W dosing after 9 months in CR

According to the provided Consort diagrams for FL and DLBCL by step-up regimen, most patients that were eligible for transition from Q2W to Q4W also did the transition. In both FL and DLBCL subjects, reasons for not doing the transition included dose delays due to AE that required subsequent dose resumption with step-up dosing and suspicion of progressive disease the timepoint for transition.

Overall, the transition to Q4W in FL and DLBCL patients does not conspicuously impact durability of response. Moreover, the clinical value of decreased frequency of dosing is acknowledged. PK data provide a rationale for de-intensification; however, clinical data are the basis of any conclusion on this matter. Although limited number of CD20-analysed samples, the available data indicate that efficacy is maintained after transition also in CD20 negative or low expression FL and DLBCL tumours.

Efficacy of odronextamab in CD20 low or negative disease

The Applicant assessed CD20 protein expression in 2 different ways:

(i) **Local assessment**, CD20 protein expression

Of 112 patients with **FL** available in the clinical database (out of a total of 128 patients [88%]), 16 patients were reported to have no detectable CD20 expression. Eight of those achieved a CR, 1 a PR, 3 had SD, 2 had PD, and 2 not evaluable.

Of the 122 patients with **DLBCL** available in the clinical database (out of a total of 127 patients [96%]), 10 patients were reported not to have CD20 expression. Of these, 2 achieved a CR, 1 a PR, 3 had PD, and 4 were not evaluable.

(ii) **Central assessment** on available tumour biopsies, CD20 protein expression

Due to limited number of available samples, the Applicant was able to centrally analyse CD20 expression by IHC in 71 (of 128) FL tumour biopsies and 33 (of 127) DLBCL biopsies.

Twenty-four patients with **FL** had less than 50% of CD20+ cells, of these 15 achieved a CR, 1 a PR, and 4 patients had SD, 2 had PD, and 2 were non-evaluable

Eight patients with **DLBCL** had less than 50% of CD20+ cells, of these 4 achieved a CR, 1 a PR, 2 had PD, and 1 was not evaluable.

Recent publications based on experiences from odronextamab and similar products point towards the importance of at least some degree of CD20 expression to enable efficacy of CD20/CD3 bispecific antibodies (*Olszewski, Blood 2024; Schuster at al, Blood 2024; Cherng et al, The Hematologist 2024; Bröske et al, Blood Adv. 2022; Brouwer-Visser et al, J Immunother Cancer 2024*), which is fully supported by the MoA of bispecific CD20/CD3 antibodies.

Thus, when a response of odronextamab treatment is observed in a patient with a tumour assessed as CD20 negative, it is most likely that some parts of the tumour actually have some degree of CD20 expression that was not caught in the available biopsy with the currently used method.

No companion diagnostic is required to assess CD20 expression prior to use of odronextamab in the pivotal studies. Thus, a positive B/R is assumed in a population where this has not been assessed.

The Applicant has agreed to further characterize the relation between CD20 expression and efficacy of odronextamab as a post authorisation recommendation (REC), by further investigating this in the ongoing confirmatory trials for DLBCL and FL respectively.

The Applicant argues that a warning in SmPC section 4.4 is not needed for patients with CD20 negative disease. This is acceptable, as data indicating clinically relevant activity is more compelling than was the case for precedents where a warning in 4.4 on this matter was instituted.

The applicant agreed to the recommendation of the CHMP and will provide further characterisation post authorisation of the relation between CD20 expression and efficacy of odronextamab – as part of to investigate this in the ongoing confirmatory trials for DLBCL and FL, respectively.

Additional efficacy data needed in the context of a conditional MA

As comprehensive data on the product are not available, a conditional marketing authorisation was requested by the applicant in the initial submission. Study R1979-ONC-22102 is a Phase 3, open label, randomized study to compare the efficacy and safety of odronextamab in combination with lenalidomide therapy versus rituximab in combination with lenalidomide (R2) therapy in participants with R/R FL and MZL in > 2 line. The analysis of odronextamab efficacy in study R1979-ONC-22102 will be tested in the FL population and in the overall indolent NHL population, which includes FL and MZL. The study is adequately powered to demonstrate efficacy in FL patients. This is considered appropriate. The primary endpoint of PFS is assessed by IRC. The final CSR will be provided by September 2031.

Study R1979-HM-2299 is a Phase 3, randomized, open label study, evaluating efficacy and safety of odronextamab versus Standard of Care (SOC) salvage therapy followed by ASCT in participants with R/R aggressive B-cell non-Hodgkin lymphoma. Participants will be randomized 1:1 to receive either odronextamab or SOC. In total, 216 patients will be enrolled in this study. The primary objective is EFS, in participants with odronextamab versus participants with SOC. While EFS including new anti-lymphoma therapy as an event, has been accepted previously in the present setting, a positive study driven by such events, and without a positive secondary PFS analysis, may be considered not to have established the efficacy of Ordspono. However, given the inclusion of non-progression elements in the EFS-definition, benefit should be corroborated by the PFS outcome.

2.6.7. Conclusions on the clinical efficacy

Clinically meaningful rates of ORR/CR, and clinically meaningful durations of responses have been shown in both DLBCL as well as FL. Despite the single-arm study design, exploratory nature of the pivotal trial, and limited sample size, the high activity of odronextamab is evident in the agreed indications. Nevertheless, the CHMP considers the following measures necessary to address the missing efficacy data in the context of a conditional MA:

- In order to provide further evidence of efficacy and safety of odronextamab in relapsed or refractory **follicular lymphoma**, the MAH will provide results from study R1979-ONC-22102, a phase 3, open label, randomised trial to compare the efficacy and safety of odronextamab in combination with lenalidomide versus rituximab in combination with lenalidomide in relapsed or refractory participants with follicular lymphoma and marginal zone lymphoma.
- In order to provide further evidence of efficacy and safety of odronextamab in relapsed or refractory **diffuse large B cell lymphoma**, the MAH will provide results from study R1979-

HM-2299, a phase 3, randomised, open-label trial evaluating the efficacy and safety of odronextamab versus Standard of Care therapy in participants with relapsed or refractory aggressive B cell non-Hodgkin Lymphoma. Due date November 2028.

2.6.8. Clinical safety

2.6.8.1. Patient exposure

Background

Study 1625 is an ongoing open-label, single-arm, multi-centre, phase 2 study of odronextamab monotherapy in patients with B-NHL; it has 5 disease-specific cohorts: R/R 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 study evaluated a 320 mg QW dose for patients with DLBCL before selecting 160 mg as the RP2D.

Study 1333 is an ongoing, first-in-human, open-label, single arm, multi-centre, phase 1 dose finding and dose escalation, and expansion 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 dose escalation phase evaluated doses from 0.03 to 320 mg QW.

There was a pause in enrolment in both studies due to a partial Clinical Hold imposed by the FDA during which the sponsor revised the step-up dosing regimen to mitigate the risk of CRS. There was an approximately 8-month interval between the last patient being enrolled in the 1/20 regimen and the first patient being enrolled in the 0.7/4/20 regimen. Thus, at the time of data cutoff, patients receiving the 1/20 regimen had the opportunity for a longer follow-up than patients receiving the 0.7/4/20 regimen.

The COVID-19 pandemic also occurred during patient enrolment into these studies and the timing of significant COVID-19 waves, lifting of restrictions, and vaccine/treatment availability varied across study regions.

For patients enrolled in the 1/20 regimen, enrolment was ongoing early in the COVID-19 pandemic (early 2020 to late 2020) when the severity of the virus was high, and no vaccines/treatments were available.

Enrolment of patients receiving the 0.7/4/20 regimen occurred later in the pandemic (mid 2021) when COVID-19 vaccines/treatments were available (to different extents in different regions); however, more transmissible strains were prevalent at the time.

An integrated safety analysis was performed for patients with FL grade 1-3a (enrolled at 80 mg QW) and for patients with DLBCL (enrolled at 160 mg QW) who had received at least 1 dose of odronextamab.

Dosing Regimens and Schedule

The intended registrational doses are 80 mg QW for patients with FL grade 1-3a and 160 mg QW for patients with DLBCL.

The step-up dosing was administered as follows:

The 1/20 regimen: Odronextamab was administered at an initial dose of 1 mg (split as 0.5 mg on cycle 1 day 1 and 0.5 mg on cycle 1 day 2), an intermediate dose of 20 mg (split as 10 mg on cycle 1 day 8 and 10 mg on cycle 1 day 9), followed by the full treatment dose of 80 mg QW (FL) or 160 mg QW (DLBCL) from cycle 1 day 15. From cycles 2 to 4, odronextamab was administered on days 1, 8, and 15 at 80 mg QW (FL) or 160 mg QW (DLBCL).

The 0.7/4/20 regimen: In view of the observed incidence of grade ≥3 CRS events, the step up regimen was modified to an initial dose of 0.7 mg (split as 0.2 mg on cycle 1 day 1 and 0.5 mg on cycle 1 day 2), an intermediate dose 1 of 4 mg (split as 2 mg on cycle 1 day 8 and 2 mg on cycle 1 day 9), and an intermediate dose 2 of 20 mg (split as 10 mg on cycle 1 day 15 and 10 mg on cycle 1 day 16). From cycle 2 to cycle 4, odronextamab was administered on days 1, 8, and 15 at 80 mg QW (for FL) or 160 mg QW (for DLBCL) Marketing approval is sought for the 0.7/4/20 regimen.

Data Pooling Strategy for Integrated Analyses

Patients from Studies 1625 and 1333 who were enrolled in the intended registrational dose cohorts (80 mg QW for FL and 160 mg QW for DLBCL) were included in a combined FL 80 mg QW Pool and a combined DLBCL 160 mg QW Pool. Patients who received at least 1 dose of odronextamab monotherapy were pooled by indication as described below:

- FL 80 mg QW Pool (N=153): All FL grade 1-3a patients enrolled in the dose group of 80 mg QW (1/20 regimen: N=74; 0.7/4/20 regimen: N=79).
- DLBCL 160 mg QW Pool (N=219): All DLBCL patients enrolled in the dose group of 160 mg QW (1/20 regimen: N=101; 0.7/4/20 regimen: N=118)

Exposure by step-up regimen, Follicular Lymphoma

Table 50: Treatment Exposure by Step-up Regimen – (Safety Analysis Set) Data cut-off date: 19 Sep 2023 Study-1333 and 20 Oct 2023 Study-1625.

	FL Grade 1-3a 1/20/80 mg (N=74)	FL Grade 1-3a 0.7/4/20/80 mg (N=79)	FL Grade 1-3a Total (N=153)
Duration of Exposure (weeks)[a]			
n	74	79	153
Mean (SD)	55.55 (48.498)	40.10 (29.760)	47.58 (40.547)
Median	42.79	31.14	38.14
Q1 : Q3	19.29 : 76.57	13.29 : 69.14	14.86 : 70.57
Min-Max	2.0 : 195.7	0.4 : 110.6	0.4 : 195.7
Duration of Exposure, n (%)			
≥4 weeks	70 (94.6%)	73 (92.4%)	143 (93.5%)
≥8 weeks	69 (93.2%)	70 (88.6%)	139 (90.8%)
≥12 weeks	66 (89.2%)	62 (78.5%)	128 (83.7%)
≥16 weeks	57 (77.0%)	56 (70.9%)	113 (73.9%)
≥20 weeks	54 (73.0%)	52 (65.8%)	106 (69.3%)
≥24 weeks	51 (68.9%)	47 (59.5%)	98 (64.1%)
≥28 weeks	45 (60.8%)	42 (53.2%)	87 (56.9%)
≥32 weeks	42 (56.8%)	39 (49.4%)	81 (52.9%)
≥36 weeks	40 (54.1%)	39 (49.4%)	79 (51.6%)
≥48 weeks	34 (45.9%)	28 (35.4%)	62 (40.5%)
Number of Doses Administered			
n	74	79	153
Mean (SD)	29.86 (17.055)	24.28 (13.280)	26.98 (15.429)
Median	28.00	24.00	24.00
Q1 : Q3	17.00 : 40.00	14.00 : 38.00	15.00 : 38.00
Min : Max	1.0 : 73.0	1.0 : 50.0	1.0 : 73.0
Number of Doses Administered, n (%)			
<6	5 (6.8%)	6 (7.6%)	11 (7.2%)
6 - <12	2 (2.7%)	10 (12.7%)	12 (7.8%)
12 - <24	28 (37.8%)	23 (29.1%)	51 (33.3%)
24 - <36	11 (14.9%)	17 (21.5%)	28 (18.3%)
36 - <48	18 (24.3%)	21 (26.6%)	39 (25.5%)
48 - <64	6 (8.1%)	2 (2.5%)	8 (5.2%)
≥64	4 (5.4%)	0	4 (2.6%)
Cumulative Dose (mg)[b]			
n	74	79	153
Mean (SD)	3193.91 (2513.266)	2188.17 (1881.081)	2674.61 (2259.125)

Median	2661.25	1808.70	2024.70
Q1 : Q3	991.00 : 4690.92	529.40 : 4264.70	744.70 : 4424.70
Min : Max	0.5 : 10099.0	0.1 : 6344.7	0.1 : 10099.0
Actual Dose Intensity (mg/week)[c]			
n	74	79	153
Mean (SD)	57.65 (20.015)	45.50 (21.343)	51.38 (21.524)
Median	60.60	52.92	57.28
Q1 : Q3	53.14 : 67.32	33.34 : 61.19	44.58 : 63.68
Min : Max	0.3 : 145.3	0.1 : 75.5	0.1 : 145.3
Relative Dose Intensity from Initial dose to first full dose (%)[d]			
n	74	79	153
Mean (SD)	479.20 (3366.953)	87.25 (26.939)	276.82 (2341.673)
Median	100.00	100.00	100.00
Q1 : Q3	56.35 : 100.00	67.51 : 100.00	59.51 : 100.00
Min : Max	17.4 : 29050.0	8.5 : 176.4	8.5 : 29050.0
Relative Dose Intensity from second full dose and beyond (%)[d]			
n	68	69	137
Mean (SD)	98.55 (4.098)	95.14 (12.858)	96.83 (9.689)
Median	100.00	100.00	100.00
Q1 : Q3	100.00 : 100.00	100.00 : 100.00	100.00 : 100.00
Min : Max	78.3 : 102.1	32.7 : 114.8	32.7 : 114.8
Relative Dose Intensity in all periods (%)[d]			
n	74	79	153
Mean (SD)	487.35 (3365.847)	90.29 (19.789)	282.33 (2341.089)
Median	100.00	100.00	100.00
Q1 : Q3	96.46 : 100.00	88.17 : 100.00	94.18 : 100.00
Min : Max	17.4 : 29050.0	8.5 : 116.3	8.5 : 29050.0

Note: [a] Duration of treatment exposure (weeks) = [minimum (date of last dose + 14, data cutoff date+1, date of death+1) - date of first dose]/7;
Duration of treatment exposure (cycles) = Cycle is defined as 21 days for the first cycles, and is 14 days from cycle 5;
Duration of treatment exposure in Patient-Year = Sum [minimum (date of last dose + 14, data cutoff date+1, date of death+1) - date of first dose]/365.25
[b] Cumulative Dose Administered is total dose of drug taken during treatment.
[c] Actual Dose Intensity is the average actual administered dose per week.
[d] Relative Dose Intensity = 100% * Actual Dose Intensity / Planned Dose Intensity.
The split doses will consider as separate doses.

Exposure by step up regimen, DLBCL

Table 51: Treatment Exposure by Step-up Regimen– (Safety Analysis Set) Data cut-off date:19 Sep 2023 Study-1333 and 20 Oct 2023 Study-1625.

	DLBCL 1/20/80 mg (N=101)	DLBCL 0.7/4/20/80 mg (N=118)	DLBCL Total (N=219)
Duration of Exposure (weeks)[a]			
n	101	118	219
Mean (SD)	28.35 (37.795)	22.01 (23.139)	24.94 (30.865)
Median	14.71	13.29	13.43
Q1 : Q3	5.14 : 30.14	6.14 : 24.00	5.29 : 27.14
Min-Max	0.7 : 176.1	0.6 : 106.3	0.6 : 176.1
Duration of Exposure, n (%)			
≥4 weeks	86 (85.1%)	101 (85.6%)	187 (85.4%)
≥8 weeks	67 (66.3%)	86 (72.9%)	153 (69.9%)
≥12 weeks	56 (55.4%)	69 (58.5%)	125 (57.1%)
≥16 weeks	48 (47.5%)	52 (44.1%)	100 (45.7%)
≥20 weeks	38 (37.6%)	44 (37.3%)	82 (37.4%)
≥24 weeks	31 (30.7%)	30 (25.4%)	61 (27.9%)
≥28 weeks	27 (26.7%)	25 (21.2%)	52 (23.7%)
≥32 weeks	25 (24.8%)	23 (19.5%)	48 (21.9%)
≥36 weeks	23 (22.8%)	20 (16.9%)	43 (19.6%)
≥48 weeks	17 (16.8%)	18 (15.3%)	35 (16.0%)
Number of Doses Administered			
n	101	118	219
Mean (SD)	17.84 (14.482)	16.64 (11.279)	17.19 (12.839)
Median	15.00	15.00	15.00
Q1 : Q3	6.00 : 22.00	8.00 : 20.00	7.00 : 21.00
Min : Max	1.0 : 65.0	1.0 : 49.0	1.0 : 65.0
Number of Doses Administered, n (%)			
<6	20 (19.8%)	18 (15.3%)	38 (17.4%)
6 - <12	20 (19.8%)	26 (22.0%)	46 (21.0%)
12 - <24	37 (36.6%)	51 (43.2%)	88 (40.2%)
24 - <36	11 (10.9%)	12 (10.2%)	23 (10.5%)
36 - <48	7 (6.9%)	9 (7.6%)	16 (7.3%)
48 - <64	5 (5.0%)	2 (1.7%)	7 (3.2%)
≥64	1 (1.0%)	0	1 (0.5%)
Cumulative Dose (mg)[b]			
n	101	118	219
Mean (SD)	3033.96 (3858.282)	2451.64 (2913.551)	2720.20 (3386.614)
Median	1481.00	1464.70	1464.70
Q1 : Q3	181.00 : 3781.00	186.70 : 3064.70	184.70 : 3221.00
Min : Max	0.5 : 17621.0	0.2 : 12024.7	0.2 : 17621.0
Actual Dose Intensity (mg/week)[c]			
n	101	118	219
Mean (SD)	86.28 (48.454)	84.15 (49.531)	85.13 (48.937)
Median	104.52	101.54	102.63
Q1 : Q3	45.25 : 121.50	39.18 : 125.86	45.25 : 124.69
Min : Max	0.3 : 149.7	0.1 : 149.8	0.1 : 149.8
Relative Dose Intensity from Initial dose to first full dose (%)[d]			
n	101	118	219
Mean (SD)	84.92 (28.956)	99.84 (70.292)	92.96 (55.606)
Median	100.00	100.00	100.00

	DLBCL 1/20/80 mg (N=101)	DLBCL 0.7/4/20/80 mg (N=118)	DLBCL Total (N=219)
Q1 : Q3	99.89 : 100.00	100.00 : 100.00	100.00 : 100.00
Min : Max	0.8 : 100.0	0.5 : 828.7	0.5 : 828.7
Relative Dose Intensity from second full dose and beyond (%)[d]			
n	75	88	163
Mean (SD)	98.33 (6.193)	98.16 (7.220)	98.24 (6.747)
Median	100.00	100.00	100.00
Q1 : Q3	100.00 : 100.00	100.00 : 100.00	100.00 : 100.00
Min : Max	58.2 : 100.0	57.2 : 112.5	57.2 : 112.5
Relative Dose Intensity in all periods (%)[d]			
n	101	118	219
Mean (SD)	87.80 (26.401)	94.13 (17.735)	91.21 (22.328)
Median	100.00	100.00	100.00
Q1 : Q3	91.89 : 100.00	100.00 : 100.00	98.94 : 100.00
Min : Max	0.8 : 100.0	0.5 : 121.8	0.5 : 121.8

Note: [a] Duration of treatment exposure (weeks) = [minimum (date of last dose + 14, data cutoff date+1, date of death+1) - date of first dose]/7;
Duration of treatment exposure (cycles) = Cycle is defined as 21 days for the first cycles, and is 14 days from cycle 5;
Duration of treatment exposure in Patient-Year = Sum [minimum (date of last dose + 14, data cutoff date+1, date of death+1) - date of first dose]/365.25
[b] Cumulative Dose Administered is total dose of drug taken during treatment.
[c] Actual Dose Intensity is the average actual administered dose per week.
[d] Relative Dose Intensity = 100% * Actual Dose Intensity / Planned Dose Intensity.
The split doses will consider as separate doses.

2.6.8.2. Adverse events

Safety data using a data cutoff of 20 Oct 2023 for Study 1625 and 19 Sep 2023 for Study 1333 are presented in the below tables.

Follicular lymphoma

Table 52: Treatment-Emergent Adverse Events by Step-up Regimen, FL Grade 1-3a 80 mg QW

	FL Grade 1-3a 1/20/80 mg (N=74)	FL Grade 1-3a 0.7/4/20/80 mg (N=79)	Total (N=153)
Number of patients with:	n (%)	n (%)	n (%)
Any TEAE	74 (100%)	79 (100%)	153 (100%)
Any NCI grade 3/4/5 TEAE	63 (85.1%)	68 (86.1%)	131 (85.6%)
Any serious TEAE	50 (67.6%)	51 (64.6%)	101 (66.0%)
Drug withdrawn due to TEAE	12 (16.2%)	9 (11.4%)	21 (13.7%)
Any TEAE leading to a dose interruption/delay	59 (79.7%)	70 (88.6%)	129 (84.3%)
Any TEAE leading to a dose reduction	8 (10.8%)	4 (5.1%)	12 (7.8%)
Any TEAE resulting in death	14 (18.9%)	6 (7.6%)	20 (13.1%)

AE, adverse event; CRS, cytokine release syndrome; FL, follicular lymphoma; MedDRA, Medical Dictionary for Regulatory Activities; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; QW, every week; TEAE, Treatment-emergent adverse event.; All AEs were coded using MedDRA Version 24.1. AE graded using NCI-CTCAE Version 4.03 in Study 1333 and Version 5.0 in Study 1625, except for CRS graded per (Lee, 2014) (Lee, 2019b). A patient is counted only once (at the highest severity) for multiple occurrences within a category.
A patient is counted only once for multiple occurrences within a category.

Table 53: Any Period: Treatment-Emergent Adverse Events in ≥10% (by PTs) of All Patients by SOC, HLT, PT, and NCI Grade (All Grades, Grades 3/4/5), FL Grade 1-3a 80 mg QW. Data cut-off date: 19 Sep 2023 Study-1333 and 20 Oct 2023 Study-1625.

	FL Grade 1-3a (N=153)	
SOC, n (%) **HLT, n (%)** **PT, n (%)**	**All Grades**	**Grades 3/4/5**
Number of patients with any TEAE, n (%)	153 (100%)	131 (85.6%)
Infections and infestations	120 (78.4%)	62 (40.5%)
Coronavirus infections	58 (37.9%)	23 (15.0%)
COVID-19	52 (34.0%)	15 (9.8%)
Lower respiratory tract and lung infections	37 (24.2%)	19 (12.4%)
Pneumonia	23 (15.0%)	16 (10.5%)
Upper respiratory tract infections	34 (22.2%)	1 (0.7%)
Upper respiratory tract infection	22 (14.4%)	0
Urinary tract infections	24 (15.7%)	5 (3.3%)
Urinary tract infection	21 (13.7%)	4 (2.6%)
Blood and lymphatic system disorders	99 (64.7%)	61 (39.9%)
Anaemias NEC	56 (36.6%)	20 (13.1%)
Anaemia	56 (36.6%)	20 (13.1%)
Neutropenias	56 (36.6%)	46 (30.1%)
Neutropenia	53 (34.6%)	43 (28.1%)
Thrombocytopenias	17 (11.1%)	5 (3.3%)
Thrombocytopenia	17 (11.1%)	5 (3.3%)
General disorders and administration site conditions	99 (64.7%)	10 (6.5%)
Febrile disorders	56 (36.6%)	3 (2.0%)
Pyrexia	56 (36.6%)	3 (2.0%)
Asthenic conditions	46 (30.1%)	7 (4.6%)
Fatigue	24 (15.7%)	4 (2.6%)
Asthenia	17 (11.1%)	3 (2.0%)
Oedema NEC	22 (14.4%)	0
Oedema peripheral	19 (12.4%)	0
Immune system disorders	95 (62.1%)	6 (3.9%)
Immune and associated conditions NEC	90 (58.8%)	6 (3.9%)
Cytokine release syndrome	89 (58.2%)	5 (3.3%)
Metabolism and nutrition disorders	86 (56.2%)	22 (14.4%)
Potassium imbalance	34 (22.2%)	8 (5.2%)
Hypokalaemia	30 (19.6%)	7 (4.6%)
Appetite disorders	21 (13.7%)	0
Decreased appetite	21 (13.7%)	0
Hyperglycaemic conditions NEC	17 (11.1%)	6 (3.9%)
Hyperglycaemia	17 (11.1%)	6 (3.9%)
Investigations	87 (56.9%)	58 (37.9%)

	FL Grade 1-3a (N=153)	
SOC, n (%) **HLT, n (%)** **PT, n (%)**	**All Grades**	**Grades 3/4/5**
Hepatobiliary function diagnostic procedures	41 (26.8%)	19 (12.4%)
Alanine aminotransferase increased	29 (19.0%)	11 (7.2%)
Aspartate aminotransferase increased	22 (14.4%)	10 (6.5%)
Gamma-glutamyltransferase increased	18 (11.8%)	6 (3.9%)
White blood cell analyses	47 (30.7%)	36 (23.5%)
Neutrophil count decreased	34 (22.2%)	26 (17.0%)
White blood cell count decreased	22 (14.4%)	11 (7.2%)
Lymphocyte count decreased	17 (11.1%)	17 (11.1%)
Platelet analyses	28 (18.3%)	11 (7.2%)
Platelet count decreased	27 (17.6%)	11 (7.2%)
Physical examination procedures and organ system status	19 (12.4%)	2 (1.3%)
Weight decreased	17 (11.1%)	2 (1.3%)
Gastrointestinal disorders	85 (55.6%)	5 (3.3%)
Diarrhoea (excl infective)	40 (26.1%)	2 (1.3%)
Diarrhoea	40 (26.1%)	2 (1.3%)
Nausea and vomiting symptoms	36 (23.5%)	0
Nausea	31 (20.3%)	0
Vomiting	17 (11.1%)	0
Gastrointestinal atonic and hypomotility disorders NEC	29 (19.0%)	0
Constipation	28 (18.3%)	0
Injury, poisoning and procedural complications	68 (44.4%)	11 (7.2%)
Non-site specific procedural complications	50 (32.7%)	7 (4.6%)
Infusion-related reaction	46 (30.1%)	7 (4.6%)
Musculoskeletal and connective tissue disorders	68 (44.4%)	5 (3.3%)
Joint related signs and symptoms	31 (20.3%)	1 (0.7%)
Arthralgia	30 (19.6%)	1 (0.7%)
Musculoskeletal and connective tissue pain and discomfort	31 (20.3%)	1 (0.7%)
Back pain	19 (12.4%)	0
Muscle pains	19 (12.4%)	0
Myalgia	19 (12.4%)	0
Skin and subcutaneous tissue disorders	63 (41.2%)	4 (2.6%)
Rashes, eruptions and exanthems NEC	37 (24.2%)	1 (0.7%)
Rash	26 (17.0%)	0
Respiratory, thoracic and mediastinal disorders	66 (43.1%)	15 (9.8%)
Coughing and associated symptoms	29 (19.0%)	0
Cough	24 (15.7%)	0
Nervous system disorders	68 (44.4%)	11 (7.2%)

	FL Grade 1-3a (N=153)	
SOC, n (%) **HLT, n (%)** **PT, n (%)**	**All Grades**	**Grades 3/4/5**
Headaches NEC	29 (19.0%)	0
Headache	28 (18.3%)	0
Psychiatric disorders	30 (19.6%)	0
Disturbances in initiating and maintaining sleep	20 (13.1%)	0
Insomnia	20 (13.1%)	0
Vascular disorders	30 (19.6%)	6 (3.9%)
Vascular hypotensive disorders	18 (11.8%)	3 (2.0%)
Hypotension	17 (11.1%)	2 (1.3%)

FL, follicular lymphoma; CRS, cytokine release syndrome; HLT, high level term; NCI-CTCAE, National Cancer Institute-Common Terminology Criteria for Adverse Events; PT, preferred term; SOC, system organ class; TEAE, Treatment-emergent adverse event.
All AEs were coded using MedDRA Version 25.1. AE graded using NCI-CTCAE Version 4.03 in Study 1333 and Version 5.0 in Study 1625, except for CRS graded per (Lee, 2014) (Lee, 2019).
A patient is counted only once (at the highest severity) for multiple occurrences within an SOC/HTL/PT.
For SOCs, the table is sorted by decreasing frequency of all grades TEAEs in the total group. Within each SOC, HLTs are sorted by decreasing frequency in the total group. Within each HLT, PTs are sorted by decreasing frequency in the total group.

DLBCL

Table 54: Treatment-Emergent Adverse Events by Step-up Regimen, DLBCL 160 mg QW

	DLBCL 1/20/160 mg (N=101)	DLBCL 0.7/4/20/160 mg (N=118)	Total (N=219)
Number of patients with:	n (%)	n (%)	n (%)
Any TEAE	101 (100%)	117 (99.2%)	218 (99.5%)
Any NCI grade 3/4/5 TEAE	87 (86.1%)	95 (80.5%)	182 (83.1%)
Any serious TEAE	66 (65.3%)	70 (59.3%)	136 (62.1%)
Drug withdrawn due to TEAE	15 (14.9%)	15 (12.7%)	30 (13.7%)
Any TEAE leading to a dose interruption/delay	70 (69.3%)	76 (64.4%)	146 (66.7%)
Any TEAE leading to a dose reduction	8 (7.9%)	0	8 (3.7%)
Any TEAE resulting in death	12 (11.9%)	18 (15.3%)	30 (13.7%)

AE, adverse event; CRS, cytokine release syndrome; DLBCL, diffuse large B-cell lymphoma; MedDRA, Medical Dictionary for Regulatory Activities; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; QW, every week; TEAE, Treatment-emergent adverse event.

All AEs were coded using MedDRA Version 24.1. AE graded using NCI-CTCAE Version 4.03 in Study 1333 and Version 5.0 in Study 1625, except for CRS graded per (Lee, 2014) (Lee, 2019b).
A patient is counted only once (at the highest severity) for multiple occurrences within a category.

Table 55: Treatment-Emergent Adverse Events in ≥10% (by PTs) of All Patients by SOC, HLT, PT and NCI Grade (All Grades, Grades 3/4/5), DLBCL 160 mg QW. Data cut-off date: 19 Sep 2023 Study-1333 and 20 Oct 2023 Study-1625.

	DLBCL (N=219)	
SOC, n (%) **HLT, n (%)** **PT, n (%)**	**All Grades**	**Grades 3/4/5**
Number of patients with any TEAE, n (%)	218 (99.5%)	182 (83.1%)
General disorders and administration site conditions	145 (66.2%)	22 (10.0%)
Febrile disorders	90 (41.1%)	7 (3.2%)
Pyrexia	90 (41.1%)	7 (3.2%)
Asthenic conditions	65 (29.7%)	7 (3.2%)
Fatigue	46 (21.0%)	4 (1.8%)
Asthenia	23 (10.5%)	4 (1.8%)
Oedema NEC	36 (16.4%)	6 (2.7%)
Oedema peripheral	30 (13.7%)	4 (1.8%)
Feelings and sensations NEC	25 (11.4%)	0
Chills	23 (10.5%)	0
Gastrointestinal disorders	135 (61.6%)	20 (9.1%)
Diarrhoea (excl infective)	51 (23.3%)	4 (1.8%)
Diarrhoea	51 (23.3%)	4 (1.8%)
Nausea and vomiting symptoms	49 (22.4%)	3 (1.4%)
Nausea	38 (17.4%)	1 (0.5%)
Vomiting	27 (12.3%)	2 (0.9%)
Gastrointestinal atonic and hypomotility disorders NEC	40 (18.3%)	0
Constipation	34 (15.5%)	0
Gastrointestinal and abdominal pains (excl oral and throat)	35 (16.0%)	6 (2.7%)
Abdominal pain	28 (12.8%)	6 (2.7%)
Infections and infestations	128 (58.4%)	76 (34.7%)
Lower respiratory tract and lung infections	36 (16.4%)	25 (11.4%)
Pneumonia	30 (13.7%)	22 (10.0%)
Coronavirus infections	34 (15.5%)	21 (9.6%)
COVID-19	31 (14.2%)	16 (7.3%)
Urinary tract infections	24 (11.0%)	5 (2.3%)
Urinary tract infection	22 (10.0%)	5 (2.3%)
Immune system disorders	127 (58.0%)	9 (4.1%)
Immune and associated conditions NEC	122 (55.7%)	9 (4.1%)
Cytokine release syndrome	121 (55.3%)	8 (3.7%)
Metabolism and nutrition disorders	126 (57.5%)	45 (20.5%)
Potassium imbalance	45 (20.5%)	17 (7.8%)

	DLBCL (N=219)	
SOC, n (%) **HLT, n (%)** **PT, n (%)**	**All Grades**	**Grades 3/4/5**
Hypokalaemia	40 (18.3%)	16 (7.3%)
Appetite disorders	37 (16.9%)	1 (0.5%)
Decreased appetite	37 (16.9%)	1 (0.5%)
Hyperglycaemic conditions NEC	31 (14.2%)	13 (5.9%)
Hyperglycaemia	31 (14.2%)	13 (5.9%)
Phosphorus metabolism disorders	29 (13.2%)	9 (4.1%)
Hypophosphataemia	28 (12.8%)	9 (4.1%)
Sodium imbalance	29 (13.2%)	7 (3.2%)
Hyponatraemia	29 (13.2%)	7 (3.2%)
Protein metabolism disorders NEC	27 (12.3%)	2 (0.9%)
Hypoalbuminaemia	22 (10.0%)	1 (0.5%)
Blood and lymphatic system disorders	125 (57.1%)	93 (42.5%)
Anaemias NEC	86 (39.3%)	49 (22.4%)
Anaemia	86 (39.3%)	49 (22.4%)
Neutropenias	46 (21.0%)	41 (18.7%)
Neutropenia	42 (19.2%)	37 (16.9%)
Thrombocytopenias	31 (14.2%)	18 (8.2%)
Thrombocytopenia	31 (14.2%)	18 (8.2%)
Investigations	111 (50.7%)	61 (27.9%)
White blood cell analyses	60 (27.4%)	47 (21.5%)
Neutrophil count decreased	37 (16.9%)	29 (13.2%)
White blood cell count decreased	26 (11.9%)	18 (8.2%)
Hepatobiliary function diagnostic procedures	43 (19.6%)	14 (6.4%)
Alanine aminotransferase increased	28 (12.8%)	7 (3.2%)
Aspartate aminotransferase increased	26 (11.9%)	6 (2.7%)
Platelet analyses	28 (12.8%)	15 (6.8%)
Platelet count decreased	28 (12.8%)	15 (6.8%)
Respiratory, thoracic and mediastinal disorders	85 (38.8%)	19 (8.7%)
Coughing and associated symptoms	51 (23.3%)	0
Cough	47 (21.5%)	0
Breathing abnormalities	27 (12.3%)	1 (0.5%)
Dyspnoea	24 (11.0%)	1 (0.5%)
Nervous system disorders	82 (37.4%)	16 (7.3%)
Headaches NEC	22 (10.0%)	1 (0.5%)

	DLBCL (N=219)	
SOC, n (%) HLT, n (%) PT, n (%)	**All Grades**	**Grades 3/4/5**
Headache	22 (10.0%)	1 (0.5%)
Injury, poisoning and procedural complications	60 (27.4%)	7 (3.2%)
Non-site specific procedural complications	31 (14.2%)	0
Infusion related reaction	30 (13.7%)	0
Vascular disorders	55 (25.1%)	14 (6.4%)
Vascular hypotensive disorders	35 (16.0%)	9 (4.1%)
Hypotension	34 (15.5%)	9 (4.1%)
Psychiatric disorders	54 (24.7%)	5 (2.3%)
Disturbances in initiating and maintaining sleep	38 (17.4%)	1 (0.5%)
Insomnia	38 (17.4%)	1 (0.5%)

DLBCL, diffuse large B cell lymphoma; CRS, cytokine release syndrome; HLT, high level term; NCI-CTCAE, National Cancer Institute-Common Terminology Criteria for Adverse Events; PT, preferred term; SOC, system organ class; TEAE, Treatment-emergent adverse event.
All AEs were coded using MedDRA Version 25.1. AE graded using NCI-CTCAE Version 4.03 in Study 1333 and Version 5.0 in Study 1625, except for CRS graded per (Lee, 2014) (Lee, 2019).
A patient is counted only once (at the highest severity) for multiple occurrences within an SOC/HTL/PT.
For SOCs, the table is sorted by decreasing frequency of all grades TEAEs in the total group. Within each SOC, HLTs are sorted by decreasing frequency in the total group. Within each HLT, PTs are sorted by decreasing frequency in the total group.

2.6.8.3. Serious adverse event/deaths/other significant events

Follicular lymphoma

Table 56: Serious Treatment-Emergent Adverse Events in ≥2% (by PTs) of All Patients by SOC, HLT, PT, and NCI Grade (All Grades, Grades 3/4/5), FL Grade 1-3a 80 mg QW. Data cut-off date: 19 Sep 2023 Study-1333 and 20 Oct 2023 Study-1625.

	FL Grade 1-3a (N=153)	
SOC, n (%) HLT, n (%) PT, n (%)	**All Grades**	**Grades 3/4/5**
Number of patients with any serious TEAE, n (%)	101 (66.0%)	80 (52.3%)
Infections and infestations	67 (43.8%)	62 (40.5%)
Coronavirus infections	25 (16.3%)	23 (15.0%)
COVID-19	16 (10.5%)	14 (9.2%)
COVID-19 pneumonia	11 (7.2%)	11 (7.2%)
Lower respiratory tract and lung infections	15 (9.8%)	15 (9.8%)
Pneumonia	13 (8.5%)	13 (8.5%)
Cytomegaloviral infections	12 (7.8%)	10 (6.5%)
Cytomegalovirus infection reactivation	5 (3.3%)	5 (3.3%)
Cytomegalovirus infection	5 (3.3%)	3 (2.0%)

SOC, n (%) HLT, n (%) PT, n (%)	FL Grade 1-3a (N=153) All Grades	 Grades 3/4/5
Urinary tract infections	5 (3.3%)	5 (3.3%)
Urinary tract infection	4 (2.6%)	4 (2.6%)
Sepsis, bacteraemia, viraemia and fungaemia NEC	6 (3.9%)	6 (3.9%)
Sepsis	4 (2.6%)	4 (2.6%)
Infections NEC	3 (2.0%)	2 (1.3%)
Respiratory tract infection	3 (2.0%)	2 (1.3%)
Pneumocystis infections	3 (2.0%)	2 (1.3%)
Pneumocystis jirovecii pneumonia	3 (2.0%)	2 (1.3%)
Immune system disorders	29 (19.0%)	6 (3.9%)
Immune and associated conditions NEC	29 (19.0%)	6 (3.9%)
Cytokine release syndrome	28 (18.3%)	5 (3.3%)
Respiratory, thoracic and mediastinal disorders	16 (10.5%)	11 (7.2%)
Lower respiratory tract inflammatory and immunologic conditions	4 (2.6%)	4 (2.6%)
Pneumonitis	4 (2.6%)	4 (2.6%)
Pulmonary thrombotic and embolic conditions	3 (2.0%)	2 (1.3%)
Pulmonary embolism	3 (2.0%)	2 (1.3%)
Injury, poisoning and procedural complications	11 (7.2%)	9 (5.9%)
Non-site specific procedural complications	6 (3.9%)	4 (2.6%)
Infusion related reaction	6 (3.9%)	4 (2.6%)
General disorders and administration site conditions	8 (5.2%)	1 (0.7%)
Febrile disorders	7 (4.6%)	1 (0.7%)
Pyrexia	7 (4.6%)	1 (0.7%)

FL, follicular lymphoma; HLT, high level term; NCI-CTCAE, National Cancer Institute-Common Terminology Criteria for Adverse Events; NEC, necrotizing enterocolitis; PT, preferred term; SOC, system organ class; TEAE, Treatment-emergent adverse event.
All AEs were coded using MedDRA Version 25.1. AE graded using NCI-CTCAE Version 4.03 in Study 1333 and Version 5.0 in Study 1625, except for CRS graded per (Lee, 2014) (Lee, 2019).
A patient is counted only once (at the highest severity) for multiple occurrences within an SOC/HLT/PT.
For SOCs, the table is sorted by decreasing frequency of all grades TEAEs in the total group. Within each SOC, HLTs are sorted by decreasing frequency in the total group. Within each HLT, PTs are sorted by decreasing frequency in the total group.

Table 57: Treatment-Emergent Adverse Events Resulting in Death by SOC, HLT, and PT, FL Grade 1-3a 80 mg QW. Data cut-off date: 19 Sep 2023 Study-1333 and 20 Oct 2023 Study-1625

SOC, n (%) HLT, n (%) PT, n (%)	FL Grade 1-3a (N=153)
Number of patients with any TEAE resulting in death, n (%)	20 (13.1%)
Infections and infestations	16 (10.5%)
Coronavirus infections	9 (5.9%)

SOC, n (%) HLT, n (%) PT, n (%)	FL Grade 1-3a (N=153)
COVID-19	5 (3.3%)
COVID-19 pneumonia	4 (2.6%)
Lower respiratory tract and lung infections	3 (2.0%)
Pneumonia	3 (2.0%)
Escherichia infections	1 (0.7%)
Escherichia sepsis	1 (0.7%)
Fungal infections NEC	1 (0.7%)
Systemic mycosis	1 (0.7%)
Polyomavirus infections	1 (0.7%)
Progressive multifocal leukoencephalopathy	1 (0.7%)
Sepsis, bacteraemia, viraemia and fungaemia NEC	1 (0.7%)
Sepsis	1 (0.7%)
Pseudomonal infection	1 (0.7%)
Pneumonia pseudomonal	1 (0.7%)
Toxoplasma infections	1 (0.7%)
Toxoplasmosis	1 (0.7%)
Cardiac disorders	2 (1.3%)
Ventricular arrhythmias and cardiac arrest	2 (1.3%)
Cardiac arrest	1 (0.7%)
Cardiorespiratory arrest	1 (0.7%)
Immune system disorders	1 (0.7%)
Immune and associated conditions NEC	1 (0.7%)
Haemophagocytic lymphohistiocytosis	1 (0.7%)
Injury, poisoning and procedural complications	1 (0.7%)
Cerebral injuries NEC	1 (0.7%)
Subarachnoid haemorrhage	1 (0.7%)

TEAE: Treatment-emergent adverse event.
All adverse events were coded using MedDRA Version 25.1. AE graded using NCI-CTCAE Version 4.03 except for CRS graded per Lee et al 2014/¬2019 in study 1333 and Version 5.0 except for CRS graded per Lee et al 2019 in study 1625.
A patient is counted only once for multiple occurrences within a system organ class/¬high level term/¬preferred term. For SOCs,¬ the table is sorted by decreasing frequency of all Grades TEAEs in the total group. Within each SOC,¬ HLTs are sorted by decreasing frequency in the total group. Within each HLT,¬ PTs are sorted by decreasing frequency in the total group.

DLBCL

Table 58: Serious Treatment-Emergent Adverse Events ≥2% (by PTs) by SOC, HLT, PT, and NCI Grade (All Grades, Grades 3/4/5), DLBCL 160 mg QW. Data cut-off date: 19 Sep 2023 Study-1333 and 20 Oct 2023 Study-1625.

	DLBCL (N=219)	
SOC, n (%) HLT, n (%) PT, n (%)	All Grades	Grades 3/4/5
Number of patients with any serious TEAE, n (%)	136 (62.1%)	100 (45.7%)

SOC, n (%) HLT, n (%) PT, n (%)	DLBCL (N=219) All Grades	 Grades 3/4/5
Infections and infestations	72 (32.9%)	66 (30.1%)
Lower respiratory tract and lung infections	23 (10.5%)	22 (10.0%)
Pneumonia	22 (10.0%)	21 (9.6%)
Coronavirus infections	22 (10.0%)	19 (8.7%)
COVID-19	16 (7.3%)	14 (6.4%)
COVID-19 pneumonia	7 (3.2%)	6 (2.7%)
Pneumocystis infections	10 (4.6%)	9 (4.1%)
Pneumocystis jirovecii pneumonia	9 (4.1%)	8 (3.7%)
Sepsis, bacteraemia, viraemia and fungaemia NEC	9 (4.1%)	8 (3.7%)
Sepsis	7 (3.2%)	7 (3.2%)
Immune system disorders	48 (21.9%)	6 (2.7%)
Immune and associated conditions NEC	48 (21.9%)	6 (2.7%)
Cytokine release syndrome	47 (21.5%)	5 (2.3%)
General disorders and administration site conditions	18 (8.2%)	6 (2.7%)
Febrile disorders	14 (6.4%)	3 (1.4%)
Pyrexia	14 (6.4%)	3 (1.4%)
Nervous system disorders	17 (7.8%)	10 (4.6%)
Encephalopathies NEC	6 (2.7%)	5 (2.3%)
Encephalopathy	6 (2.7%)	5 (2.3%)

DLBCL, diffuse large B cell lymphoma; HLT, high level term; NCI-CTCAE, National Cancer Institute-Common Terminology Criteria for Adverse Events; NEC, necrotizing enterocolitis; PT, preferred term; SOC, system organ class; TEAE, Treatment-emergent adverse event.
All AEs were coded using MedDRA Version 25.1. AE graded using NCI-CTCAE Version 4.03 in Study 1333 and Version 5.0 in Study 1625, except for CRS graded per (Lee, 2014) (Lee, 2019).
A patient is counted only once (at the highest severity) for multiple occurrences within an SOC/HLT/PT.
For SOCs, the table is sorted by decreasing frequency of all grades TEAEs in the total group. Within each SOC, HLTs are sorted by decreasing frequency in the total group. Within each HLT, PTs are sorted by decreasing frequency in the total group.

Table 59: Treatment-Emergent Adverse Events Resulting in Death by SOC, HLT and PT, DLBCL 160 mg QW. Data cut-off date: 19 Sep 2023 Study-1333 and 20 Oct 2023 Study-1625.

SOC, n (%) HLT, n (%) PT, n (%)	DLBCL (N=219)
Number of patients with any TEAE resulting in death, n (%)	30 (13.7%)
Infections and infestations	21 (9.6%)
Coronavirus infections	8 (3.7%)
COVID-19	6 (2.7%)
COVID-19 pneumonia	2 (0.9%)
Lower respiratory tract and lung infections	4 (1.8%)
Pneumonia	4 (1.8%)
Sepsis, bacteraemia, viraemia and fungaemia NEC	3 (1.4%)

SOC, n (%) HLT, n (%) PT, n (%)	DLBCL (N=219)
Sepsis	3 (1.4%)
Cytomegaloviral infections	2 (0.9%)
Cytomegalovirus infection	1 (0.5%)
Cytomegalovirus infection reactivation	1 (0.5%)
Pneumonia cytomegaloviral	1 (0.5%)
Fungal infections NEC	1 (0.5%)
Pneumonia fungal	1 (0.5%)
Pneumocystis infections	1 (0.5%)
Pneumocystis jirovecii pneumonia	1 (0.5%)
Pseudomonal infection	1 (0.5%)
Pseudomonal sepsis	1 (0.5%)
Respiratory syncytial viral infections	1 (0.5%)
Respiratory syncytial virus bronchitis	1 (0.5%)
General disorders and administration site conditions	3 (1.4%)
General signs and symptoms NEC	2 (0.9%)
General physical health deterioration	1 (0.5%)
Multiple organ dysfunction syndrome	1 (0.5%)
Death and sudden death	1 (0.5%)
Death	1 (0.5%)
Respiratory, thoracic and mediastinal disorders	2 (0.9%)
Parenchymal lung disorders NEC	2 (0.9%)
Interstitial lung disease	2 (0.9%)
Cardiac disorders	1 (0.5%)
Supraventricular arrhythmias	1 (0.5%)
Atrial fibrillation	1 (0.5%)
Gastrointestinal disorders	1 (0.5%)
Intestinal haemorrhages	1 (0.5%)
Rectal haemorrhage	1 (0.5%)
Immune system disorders	1 (0.5%)
Immune and associated conditions NEC	1 (0.5%)
Haemophagocytic lymphohistiocytosis	1 (0.5%)
Injury, poisoning and procedural complications	1 (0.5%)
Cerebral injuries NEC	1 (0.5%)
Brain herniation	1 (0.5%)
Metabolism and nutrition disorders	1 (0.5%)
Metabolic disorders NEC	1 (0.5%)
Metabolic disorder	1 (0.5%)

TEAE: Treatment-emergent adverse event.
All adverse events were coded using MedDRA Version 25.1. AE graded using NCI-CTCAE Version 4.03 except for CRS graded per Lee et al 2014/¬2019 in study 1333 and Version 5.0 except for CRS graded per Lee et al 2019 in study 1625.

A patient is counted only once for multiple occurrences within a system organ class/high level term/preferred term. For SOCs, the table is sorted by decreasing frequency of all Grades TEAEs in the total group. Within each SOC,HLTs are sorted by decreasing frequency in the total group. Within each HLT, PTs are sorted by decreasing frequency in the total group.

2.6.8.4. Adverse events of special interest (AESI)

Cytokine Release Syndrome

CRS is a disorder characterized 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.

There is significant overlap in the clinical presentation of CRS and IRR, both of which may include fever, rigors, tachycardia, hypotension, hypoxia, and bronchospasm. The symptomatology associated with both entities is consistent with an underlying mechanism of exaggerated immune response and release of inflammatory cytokines.

In the protocols of Studies 1625 and 1333, CRS was defined as an event associated with typical signs and symptoms that occurred 6 or more hours from the start of the infusion or more than 2 hours after completion of the infusion (whichever is later).

IRR was defined as any AE that occurs during the infusion, or within 2 hours after completion of the infusion, and is associated with typical signs and symptoms. Investigators, at their discretion, could report IRR or CRS regardless of time of onset based on clinical judgment.

Follicular lymphoma

Table 60: Treatment-Emergent CRS by Each Severity Grade (Grades 1, 2, 3, 4, 5), FL Grade 1-3a 80 mg QW. Data cut-off date: 19 Sep 2023 Study-1333 and 20 Oct 2023 Study-1625.

PT, n (%)	FL Grade 1-3a 1/20/80 mg (N=74)	FL Grade 1-3a 0.7/4/20/80 mg (N=79)
Number of patients with at least 1 CRS, n (%)	43 (58.1%)	46 (58.2%)
Grade 1	24 (32.4%)	37 (46.8%)
Grade 2	15 (20.3%)	8 (10.1%)
Grade 3	4 (5.4%)	1 (1.3%)
Grade 4	0	0
Grade 5	0	0

CRS, cytokine release syndrome; FL, follicular lymphoma; PT, preferred term; QW, every week.

For the management of CRS in the 1/20 regimen, 10/74 (13.5%) patients received tocilizumab, 13/74 (17.6%) patients received systemic steroids, 10/74 (13.5%) patients received IV fluid bolus and low flow oxygen (each), 4/74 (5.4%) patients received vasopressors, and 1/74 (1.4%) patient received high flow oxygen.

In the 0.7/4/20 regimen, 16/79 (20.3%) patients received tocilizumab, 27/79 (34.2%) patients received systemic steroids, 1/79 (1.3%) patient received vasopressors, 7/79 (8.9%) patients received IV fluid bolus, and 4/79 (5.1%) patients received low flow oxygen. No patient received high flow oxygen in the 0.7/4/20 regimen.

No patients in either step-up regimen received mechanical ventilation.

DLBCL

Table 61: Treatment-Emergent CRS by Each Severity Grade (Grades 1, 2, 3, 4, 5), DLBCL 160 mg QW. Data cut-off date: 19 Sep 2023 Study-1333 and 20 Oct 2023 Study-1625.

PT, n (%)	DLBCL 1/20/160 mg (N=101)	DLBCL 0.7/4/20/160 mg (N=118)
Number of patients with at least 1 CRS, n (%)	60 (59.4%)	61 (51.7%)
Grade 1	31 (30.7%)	41 (34.7%)
Grade 2	22 (21.8%)	19 (16.1%)
Grade 3	7 (6.9%)	1 (0.8%)
Grade 4	0	0
Grade 5	0	0

CRS, cytokine release syndrome; PT, preferred term; QW, every week

For the management of CRS in the 1/20 regimen, 19/101 (18.8%) patients received systemic steroids, 15/101 (14.9%) patients received tocilizumab, 6/101 (5.9%) patients received vasopressors, 19/101 (18.8%) patients received IV fluid bolus, 2/101 (2.0%) patients received high flow oxygen, and 9/101 (8.9%) patients received low flow oxygen.

In the 0.7/4/20 regimen, 31/118 (26.3%) patients received tocilizumab, 24/118 (20.3%) patients received systemic steroids, 1/118 (0.8%) patient received vasopressors, 12/118 (10.2%) patients received IV fluid bolus, and 11/118 (9.3%) patients required low flow oxygen. No patient received high flow oxygen in the 0.7/4/20 regimen.

No patients in either step-up regimen received mechanical ventilation.

FL and DLBCL (data update)

As of the cutoff of 20 Oct 2023 for Study 1625 and 19 Sept 2023 for Study 1333 a total of 197 patients with FL and DLBCL indication have been treated with the 0.7/4/20 mg step up regimen (Table 64). There were no grade 4 or 5 CRS events and no patients required mechanical ventilation to treat CRS events.

Table 62: Incidence of CRS by Step-up Regimen and Each Grade in Patients with FL 80 mg and DLBCL 160 mg

	1/20 mg step-up regimen N=175	0.7/4/20 mg step-up regimen N=197
Any Grade	103 (58.9%)	107 (54.3%)
Grade 1	55 (31.4%)	78 (39.6%)
Grade 2	37 (21.1%)	27 (13.7%)
Grade 3	11 (6.3%)	2 (1.0%)
Grade 4	0	0
Grade 5	0	0

Study 1625 data cut-off date is Oct 20, 2023. Study 1333 data cut-off date is Sep 19, 2023
All adverse events were coded using MedDRA Version 25.1. AE graded using NCI-CTCAE Version 4.03 except for CRS graded per Lee et al 2014/2019 in study 1333 and Version
5.0 except for CRS graded per Lee et al 2019 in study 1625.

The modifications in the step-up regimen together with enhanced premedication were successful in mitigating the risk of CRS in patients with FL grade 1-3a and DLBCL. Twenty nine patients (14.7%, 29/197) patients experienced grade ≥2 CRS in the 0.7/4/20 mg step-up regimen compared with 27.4% (48/175) patients in the 1/20 mg step-up regimen. There was an increased use of immunosuppressants during step-up (dexamethasone IV: 20 mg x 2 and dexamethasone PO: 10 mg x

8). The proposed dosing regimen as presented in the SmPC reflects both the revised step-up regimen and the revised premedication guidance.

Table 65 compares the Period 1 incidence of AEs that may be associated with increased steroid use. (Period 1 is defined as the time from the initial dose through the first full dose, including the duration prior to second full dose). There were no significant differences in the incidence of hypertension, gastrointestinal bleeding, or severe infections between the patients receiving the 1/20 mg step-up regimen and the 0.7/4/20 mg step-up regimen (Table 65). Hyperglycaemia was more frequently reported during Period 1 in patients who received the 0.7/4/20 mg step-up, and with both regimens the events were predominantly transient, grade 1 or 2, and patients were able to continue on treatment with odronextamab.

Table 63: Incidence of TEAEs During Step up[a] That may be Associated with Steroid Use

	FL 80 mg (N=153)		**DLBCL 160 mg (N=219)**	
	1/20 mg (N=74)	**0.7/4/20 mg (N=79)**	**1/20 mg (N=101)**	**0.7/4/20 mg (N=118)**
Grade ≥3 infection	8 (10.8%)	6 (7.6%)	9 (8.9%)	13 (11.0%)
Hyperglycaemia	6 (8.1%)	10 (12.7%)	4 (4.0%)	18 (15.3%)
Hypertension	2 (2.7%)	1 (1.3%)	3 (3.0%)	4 (3.4%)
Gastrointestinal bleeding	0	0	0	0

[a] The time from the initial dose through the first full dose (including the duration prior to second full dose)

The rates of severe infections (grade 3 and higher) were similar between the 1/20 mg step-up regimen and the 0.7/4/20 mg regimen during Period 1 for both FL (10.8% in 1/20 mg and 7.6% in 0.7/4/20 mg) and DLBCL (8.9% in 1/20 mg and 11.0% in 0.7/4/20 mg), indicating that the difference in steroid use during step-up dosing did not have an impact on severe infections.

IRR

The most common presenting signs and symptoms of IRR occurring in ≥5% of patients in either step-up regimen were Pyrexia, Chills, Hypotension, Tachycardia, and Hypoxia.

Follicular lymphoma

Table 64: Treatment-Emergent IRR by Each Severity Grade (Grades 1, 2, 3, 4, 5), 0.7/4/20 Regimen by Dosing Period, FL Grade 1-3a 80 mg QW. Data cut-off date: 19 Sep 2023 Study-1333 and 20 Oct 2023 Study-1625.

	Period 1				Period 1 Total	Period 2 Total	
PT, n (%)	Initial Dose (N=79)	Intermediate Dose I (N=75)	Intermediate Dose II (N=74)	First Full Dose (N=70)	Initial Dose to First Full Dose (N=79)	Second Full Dose and beyond (N=69)	Any Period (N=79)
Number of patients with at least 1 IRR, n (%)	16 (20.3%)	7 (9.3%)	3 (4.1%)	0	**20 (25.3%)**	0	**20 (25.3%)**
Grade 1	4 (5.1%)	2 (2.7%)	0	0	**4 (5.1%)**	0	**4 (5.1%)**
Grade 2	11 (13.9%)	3 (4.0%)	3 (4.1%)	0	**13 (16.5%)**	0	**13 (16.5%)**
Grade 3	1 (1.3%)	2 (2.7%)	0	0	**3 (3.8%)**	0	**3 (3.8%)**
Grade 4	0	0	0	0	**0**	0	**0**
Grade 5	0	0	0	0	**0**	0	**0**

IRR, infusion-related reaction; FL, follicular lymphoma; PT, preferred term; QW, every week.
Only treatment-related IRR were included for analysis as some IRR were specifically related to other concomitant medications received during the study.
Initial dose period: From week 1 dose to prior to week 2 dose.
Intermediate dose period: From week 2 dose to prior to the first full dose.
First full dose period: The first full dose is defined as the first weekly total dose that is ≥90% * target dose at week 3 or later. This period is from the first full dose to prior to the second full dose.
Second full dose and beyond: The second full dose is defined as any dose after the first full dose regardless of dosage. This period is from the second full dose and beyond.

DLBCL

Table 65: Treatment-Emergent IRR by Each Severity Grade (Grades 1, 2, 3, 4, 5), 0.7/4/20 Regimen by Dosing Period, DLBCL 160 mg QW. Data cut-off date: 19 Sep 2023 Study-1333 and 20 Oct 2023 Study-1625.

	Period 1				Period 1 Total	Period 2 Total	
	Initial Dose (N=118)	Intermediate Dose I (N=111)	Intermediate Dose II (N=104)	First Full Dose (N=94)	Initial Dose to First Full Dose (N=118)	Second Full Dose and beyond (N=88)	Any Period (N=118)
Number of patients with at least 1 IRR, n (%)	5 (4.2%)	2 (1.8%)	0	0	**7 (5.9%)**	1 (1.1%)	**7 (5.9%)**
Grade 1	3 (2.5%)	1 (0.9%)	0	0	**4 (3.4%)**	1 (1.1%)	**4 (3.4%)**
Grade 2	2 (1.7%)	1 (0.9%)	0	0	**3 (2.5%)**	0	**3 (2.5%)**
Grade 3	0	0	0	0	**0**	0	**0**
Grade 4	0	0	0	0	**0**	0	**0**
Grade 5	0	0	0	0	**0**	0	**0**

IRR, infusion-related reaction; DLBCL, diffuse large B-cell lymphoma; QW, every week.
Only treatment-related IRR were included for analysis as some IRR were specifically related to other concomitant medications received during the study.
Initial dose period: From week 1 dose to prior to week 2 dose.
Intermediate dose period: From week 2 dose to prior to the first full dose.

First full dose period: The first full dose is defined as the first weekly total dose that is ≥90% * target dose at week 3 or later. This period is from the first full dose to prior to the second full dose.
Second full dose and beyond: The second full dose is defined as any dose after the first full dose regardless of dosage. This period is from the second full dose and beyond.

Immune effector cell-associated neurotoxicity syndrome (ICANS)

Follicular lymphoma

The incidence of neurotoxicity (including ICANS) was 44.4%. The incidence of grade ≥3 neurotoxicity events was 6.5%. No patients experienced a grade 4 or 5 event.

DLBCL

The incidence of neurotoxicity (including ICANS) was 39.3%. The incidence of neurotoxicity events grade 3 or 4 was 7.3%

Three of 219 (1.4%) patients with DLBCL had grade 4 events. These events were Encephalopathy, Cerebral Hemorhage, and Brain edema. One of these (Encephalopathy) was considered treatment related by the investigator. The event was confounded by overlapping anorexia, electrolyte abnormalities and metabolic disorder following a recent infection.

Tumour lysis syndrome (TLS)

In the FL+DLBCL Combined Pool, 2/175 (1.1%) patients receiving the 1/20 regimen had grade ≥3 events of TLS, which occurred during the ramp-up towards the target dose.

2.6.8.5. Laboratory findings

Follicular lymphoma

Table 66: New or Worsened Laboratory Results by NCI-CTCAE for Hematology in FL Patients 80 mg QW Pool – (Safety Analysis Set). Data cut-off date: 19 Sep 2023 Study-1333 and 20 Oct 2023 Study-1625.

	Total (N=153)		
Parameter (CTCAE Term)	**All Grades**	**Grades 3/4**	**Grade 4**
Number of patients with at least one lab abnormality, n (%)	151/153 (98.7%)	137/153 (89.5%)	110/153 (71.9%)
Hemoglobin (Anemia)	118/153 (77.1%)	24/153 (15.7%)	0/153
Leukocytes (White blood cell decreased)	98/153 (64.1%)	42/153 (27.5%)	10/153 (6.5%)
Lymphocytes (Lymphocyte count decreased)	134/153 (87.6%)	126/153 (82.4%)	98/153 (64.1%)
Lymphocytes (Lymphocyte count increased)	29/153 (19.0%)	0/153	0/153
Neutrophils (Neutrophil count decreased)	106/153 (69.3%)	73/153 (47.7%)	34/153 (22.2%)
Platelets (Platelet count decreased)	82/153 (53.6%)	20/153 (13.1%)	5/153 (3.3%)

FL, Follicular lymphoma; NCI-CTCAE, National Cancer Institute-Common Terminology Criteria for Adverse Events; QW, every week.
NCI grades were coded using CTCAE Version 4.03 in Study 1333 and Version 5.0 in Study 1625.
Percentages are based on the number of patients with at least one post-baseline value available for that parameter.
Post-baseline value is for on-treatment period only.
A patient is counted only once for multiple occurrences for the same parameter.

Table 6769: New or Worsened Laboratory Results by NCI-CTCAE for Liver Function in FL Patients 80 mg QW Pool by Step-up Regimen – (Safety Analysis Set). Data cut-off date: 19 Sep 2023 Study-1333 and 20 Oct 2023 Study-1625.

Parameter (CTCAE Term)	FL Grade 1-3a 1/20/80 mg (N=74)			FL Grade 1-3a 0.7/4/20/80 mg (N=79)			Total (N=153)		
	All Grades	Grades 3/4	Grade 4	All Grades	Grades 3/4	Grade 4	All Grades	Grades ¾	Grade 4
Number of patients with at least one lab abnormality, n (%)	65/74 (87.8%)	21/74 (28.4%)	4/74 (5.4%)	75/79 (94.9%)	13/79 (16.5%)	2/79 (2.5%)	140/153 (91.5%)	34/153 (22.2%)	6/153 (3.9%)
Alanine Aminotransferase (Alanine aminotransferase increased)	42/74 (56.8%)	19/74 (25.7%)	2/74 (2.7%)	44/79 (55.7%)	4/79 (5.1%)	1/79 (1.3%)	86/153 (56.2%)	23/153 (15.0%)	3/153 (2.0%)
Albumin (Hypoalbuminemia)	48/73 (65.8%)	1/73 (1.4%)	0/73	53/79 (67.1%)	2/79 (2.5%)	0/79	101/152 (66.4%)	3/152 (2.0%)	0/152
Alkaline Phosphatase (Alkaline phosphatase increased)	28/74 (37.8%)	0/74	0/74	23/79 (29.1%)	2/79 (2.5%)	0/79	51/153 (33.3%)	2/153 (1.3%)	0/153
Aspartate Aminotransferase (Aspartate aminotransferase increased)	45/74 (60.8%)	17/74 (23.0%)	4/74 (5.4%)	41/79 (51.9%)	6/79 (7.6%)	1/79 (1.3%)	86/153 (56.2%)	23/153 (15.0%)	5/153 (3.3%)
Bilirubin (Blood bilirubin increased)	15/74 (20.3%)	3/74 (4.1%)	0/74	20/79 (25.3%)	2/79 (2.5%)	1/79 (1.3%)	35/153 (22.9%)	5/153 (3.3%)	1/153 (0.7%)

FL, Follicular lymphoma; NCI-CTCAE, National Cancer Institute-Common Terminology Criteria for Adverse Events; QW, every week.
NCI grades were coded using CTCAE Version 4.03 in Study 1333 and Version 5.0 in Study 1625.
Percentages are based on the number of patients with at least one post-baseline value available for that parameter.
Post-baseline value is for on-treatment period only.
A patient is counted only once for multiple occurrences for the same parameter.

DLBCL

Table 6870: New or Worsened Laboratory Results by NCI-CTCAE Grade for Hematology in DLBCL Patients 160 mg QW Pool – (Safety Analysis Set). Data cut-off date: 19 Sep 2023 Study-1333 and 20 Oct 2023 Study-1625.

Parameter (CTCAE Term)	Total (N=219)		
	All Grades	Grades ¾	Grade 4
Number of patients with at least one lab abnormality, n (%)	218/219 (99.5%)	206/219 (94.1%)	150/219 (68.5%)
Hemoglobin (Anemia)	162/219 (74.0%)	77/219 (35.2%)	0/219
Leukocytes (White blood cell decreased)	136/219 (62.1%)	70/219 (32.0%)	15/219 (6.8%)
Lymphocytes (Lymphocyte count decreased)	183/218 (83.9%)	173/218 (79.4%)	125/218 (57.3%)
Lymphocytes (Lymphocyte count increased)	35/218 (16.1%)	0/218	0/218
Neutrophils (Neutrophil count decreased)	130/219 (59.4%)	79/219 (36.1%)	38/219 (17.4%)
Platelets (Platelet count decreased)	127/219 (58.0%)	55/219 (25.1%)	29/219 (13.2%)

DLBCL, Diffuse large B-cell lymphoma; NCI-CTCAE, National Cancer Institute-Common Terminology Criteria for Adverse Events; QW, every week.
NCI grades were coded using CTCAE Version 4.03 in Study 1333 and Version 5.0 in Study 1625.
Percentages are based on the number of patients with at least one post-baseline value available for that parameter.
Post-baseline value is for on-treatment period only.
A patient is counted only once for multiple occurrences for the same parameter.

Table 69: New or Worsened Laboratory Results by NCI-CTCAE Grade for Liver Function in DLBCL Patients 160 mg QW Pool by Step-up Regimen – (Safety Analysis Set). Data cut-off date: 19 Sep 2023 Study-1333 and 20 Oct 2023 Study-1625.

Parameter (CTCAE Term)	DLBCL 1/20/160 mg (N=101)			DLBCL 0.7/4/20/160 mg (N=118)			Total (N=219)		
	All Grades	Grades 3/4	Grade 4	All Grades	Grades ¾	Grade 4	All Grades	Grades 3/4	Grade 4
Number of patients with at least 1 lab abnormality, n (%)	91/101 (90.1%)	13/101 (12.9%)	2/101 (2.0%)	103/118 (87.3%)	15/118 (12.7%)	2/118 (1.7%)	194/219 (88.6%)	28/219 (12.8%)	4/219 (1.8%)
Alanine Aminotransferase (Alanine aminotransferase increased)	44/101 (43.6%)	6/101 (5.9%)	2/101 (2.0%)	56/118 (47.5%)	3/118 (2.5%)	1/118 (0.8%)	100/219 (45.7%)	9/219 (4.1%)	3/219 (1.4%)
Albumin (Hypoalbuminemia)	71/101 (70.3%)	2/101 (2.0%)	0/101	81/118 (68.6%)	3/118 (2.5%)	0/118	152/219 (69.4%)	5/219 (2.3%)	0/219
Alkaline Phosphatase (Alkaline phosphatase increased)	39/101 (38.6%)	3/101 (3.0%)	0/101	46/118 (39.0%)	3/118 (2.5%)	0/118	85/219 (38.8%)	6/219 (2.7%)	0/219
Aspartate Aminotransferase (Aspartate aminotransferase increased)	55/101 (54.5%)	7/101 (6.9%)	1/101 (1.0%)	61/118 (51.7%)	3/118 (2.5%)	1/118 (0.8%)	116/219 (53.0%)	10/219 (4.6%)	2/219 (0.9%)
Bilirubin (Blood bilirubin increased)	19/101 (18.8%)	2/101 (2.0%)	0/101	26/118 (22.0%)	6/118 (5.1%)	0/118	45/219 (20.5%)	8/219 (3.7%)	0/219

DLBCL, Diffuse large B-cell lymphoma; NCI-CTCAE, National Cancer Institute-Common Terminology Criteria for Adverse Events; QW, every week.
NCI grades were coded using CTCAE Version 4.03 in Study 1333 and Version 5.0 in Study 1625.
Percentages are based on the number of patients with at least one post-baseline value available for that parameter.
Post-baseline value is for on-treatment period only.
A patient is counted only once for multiple occurrences for the same parameter.

2.6.8.6. In vitro biomarker test for patient selection for safety

N/A

2.6.8.7. Safety in special populations

There are no meaningful differences in safety by the age brackets given below.

Table 70 – Summary of Treatment-Related Treatment-Emergent Adverse Events by Age Group. FL Grade 1-3a 80mg QW. Data cut-off date: 19 Sep 2023 Study-1333 and 20 Oct 2023 Study-1625

	Age: <65 years (N=91)	Age: >= 65 to < 75 years (N=46)	Age: >= 75 years (N=16)	Total (N=153)
Number of treatment-related TEAEs	1161	432	84	1677
Number of NCI grade 3/ 4/ 5 treatment-related TEAEs	189	96	24	309

Number of serious treatment-related TEAEs	71	41	7	119
Number of patients with any treatment-related TEAE, n (%)	87 (95.6%)	44 (95.7%)	12 (75.0%)	143 (93.5%)
Number of patients with any NCI grade 3/ 4/ 5 treatment-related TEAE, n (%)	63 (69.2%)	31 (67.4%)	8 (50.0%)	102 (66.7%)
Number of patients with any serious treatment-related TEAE, n (%)	39 (42.9%)	24 (52.2%)	5 (31.3%)	68 (44.4%)
Number of patients with drug withdrawn due to treatment-related TEAEs, n (%)	7 (7.7%)	3 (6.5%)	1 (6.3%)	11 (7.2%)
Number of patients with any treatment-related TEAE leading to a dose interruption/ delay, n (%)	61 (67.0%)	31 (67.4%)	8 (50.0%)	100 (65.4%)
Number of patients with any treatment-related TEAE leading to a dose reduction, n (%)	7 (7.7%)	5 (10.9%)	0	12 (7.8%)
Number of patients with any treatment-related TEAE resulting in death, n (%)	2 (2.2%)	3 (6.5%)	0	5 (3.3%)

TEAE: Treatment-emergent adverse event.

All adverse events were coded using MedDRA Version 25.1. AE graded using NCI-CTCAE Version 4.03 except for CRS graded per Lee et al 2014/ 2019 in study 1333 and Version 5.0 except for CRS graded per Lee et al 2019 in study 1625.
A patient is counted only once for multiple occurrences within a category.

Table 71– Summary of Treatment-Related Treatment-Emergent Adverse Events by Age Group. DLBCL 160mg QW. Data cut-off date: 19 Sep 2023 Study-1333 and 20 Oct 2023 Study-1625

	Age: <65 years (N=100)	Age: >= 65 to < 75 years (N=76)	Age: >= 75 years (N=43)	Total (N=219)
Number of treatment-related TEAEs	1030	551	304	1885
Number of NCI grade 3/ 4/ 5 treatment-related TEAEs	214	130	69	413
Number of serious treatment-related TEAEs	102	65	37	204
Number of patients with any treatment-related TEAE, n (%)	90 (90.0%)	69 (90.8%)	38 (88.4%)	197 (90.0%)
Number of patients with any NCI grade 3/ 4/ 5 treatment-related TEAE, n (%)	62 (62.0%)	41 (53.9%)	21 (48.8%)	124 (56.6%)

Number of patients with any serious treatment-related TEAE, n (%)	51 (51.0%)	31 (40.8%)	21 (48.8%)	103 (47.0%)
Number of patients with drug withdrawn due to treatment-related TEAEs, n (%)	10 (10.0%)	7 (9.2%)	4 (9.3%)	21 (9.6%)
Number of patients with any treatment-related TEAE leading to a dose interruption/ delay, n (%)	45 (45.0%)	41 (53.9%)	24 (55.8%)	110 (50.2%)
Number of patients with any treatment-related TEAE leading to a dose reduction, n (%)	5 (5.0%)	1 (1.3%)	2 (4.7%)	8 (3.7%)
Number of patients with any treatment-related TEAE resulting in death, n (%)	6 (6.0%)	4 (5.3%)	2 (4.7%)	12 (5.5%)

Study 1625 data cut-off date is Oct 20th, 2023. Study 1333 data cut-off date is Sep 19th, 2023.
TEAE: Treatment-emergent adverse event.

All adverse events were coded using MedDRA Version 25.1. AE graded using NCI-CTCAE Version 4.03 except for CRS graded per Lee et al 2014/ 2019 in study 1333 and Version 5.0 except for CRS graded per Lee et al 2019 in study 1625.
A patient is counted only once for multiple occurrences within a category.

Table 72: TEAE by age group – FL 80mg and DLBCL 160 mg

MedDRA Terms	Age <65 Number (Percentage) N= 191	Age 65-74 Number (Percentage) N=122	Age 75-84 Number (Percentage) N= 55	Age 85+ Number (Percentage) N=4
Total AEs Total number of patients with TEAE	190 (99.5%)	122 (100%)	55 (100%)	4 (100%)
Serious AEs – Total Patients	116 (60.7%)	81 (66.4%)	36 (65.5%)	4 (100%)
- Fatal	23 (12.0%)	17 (13.9%)	10 (18.2%)	0
- Hospitalization/prolong existing hospitalization	112 (58.6%)	79 (64.8%)	32 (58.2%)	4 (100%)
- Life-threatening	16 (8.4%)	11 (9.0%)	3 (5.5%)	0
- Disability/incapacity	1 (0.5%)	4 (3.3%)	0	0
- Other (medically significant)	12 (6.3%)	8 (6.6%)	7 (12.7%)	0
AE leading to drop-out**	28 (14.7%)	16 (13.1%)	6 (10.9%)	1 (25.0%)
Psychiatric disorders SOC	31 (16.2%)	37 (30.3%)	16 (29.1%)	0
Nervous system disorders SOC	75 (39.3%)	49 (40.2%)	23 (41.8%)	3 (75.0%)
Accidents and injuries SMQ (broad)	2 (1.0%)	3 (2.5%)	1 (1.8%)	1 (25.0%)
Cardiac disorders SOC	36 (18.8%)	28 (23.0%)	13 (23.6%)	0
Vascular disorders SOC	33 (17.3%)	35 (28.7%)	16 (29.1%)	1 (25.0%)
Cerebrovascular disorders PT	0	0	0	0

MedDRA Terms	Age <65 Number (Percentage) N= 191	Age 65-74 Number (Percentage) N=122	Age 75-84 Number (Percentage) N= 55	Age 85+ Number (Percentage) N=4
Infections and infestations SOC	130 (68.1%)	82 (67.2%)	34 (61.8%)	2 (50.0%)
Anticholinergic syndrome SMQ (broad)	93 (48.7%)	64 (52.5%)	29 (52.7%)	2 (50.0%)
Quality of life decreased PT	0	0	0	0
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures***	23 (12.0%)	25 (20.5%)	12 (21.8%)	1 (25.0%)
Other AE appearing more frequently in older patients (>5% difference by PT, not including 85+N):				
Cytomegalovirus infection reactivation	7 (3.7%)	9 (7.4%)	6 (10.9%)	0
Oral candidiasis	4 (2.1%)	4 (3.3%)	4 (7.3%)	1 (25.0%)
Cellulitis	0	1 (0.8%)	3 (5.5%)	0
Oedema peripheral	21 (11.0%)	22 (18.0%)	6 (10.9%)	0
Asthenia	18 (9.4%)	12 (9.8%)	10 (18.2%)	0
Pain	0	2 (1.6%)	4 (7.3%)	0
Lymphopenia	4 (2.1%)	3 (2.5%)	4 (7.3%)	0
Diarrhoea	42 (22.0%)	36 (29.5%)	13 (23.6%)	0
Nausea	31 (16.2%)	23 (18.9%)	15 (27.3%)	0
Constipation	22 (11.5%)	29 (23.8%)	10 (18.2%)	1 (25.0%)
Abdominal pain	14 (7.3%)	19 (15.6%)	4 (7.3%)	0
Haemoglobin decreased	0	1 (0.8%)	3 (5.5%)	0
Decreased appetite	23 (12.0%)	22 (18.0%)	11 (20.0%)	2 (50.0%)
Hyperglcaemia	20 (10.5%)	15 (12.3%)	12 (21.8%)	1 (25.0%)
Hypomagnesaemia	12 (6.3%)	14 (11.5%)	2 (3.6%)	0
Hypoxia	6 (3.1%)	3 (2.5%)	7 (12.7%)	0
Pruritus	17 (8.9%)	10 (8.2%)	9 (16.4%)	0
Back pain	11 (5.8%)	21 (17.2%)	8 (14.5%)	0
Fall	5 (2.6%)	9 (7.4%)	5 (9.1%)	1 (25.0%)
Atrial fibrillation	5 (2.6%)	8 (6.6%)	7 (12.7%)	0
Hypotension	18 (9.4%)	24 (19.7%)	8 (14.5%)	1 (25.0%)
Hypertension	7 (3.7%)	5 (4.1%)	5 (9.1%)	0
Insomnia	26 (13.6%)	23 (18.9%)	9 (16.4%)	0

MedDRA Terms	Age <65 Number (Percentage) N= 191	Age 65-74 Number (Percentage) N=122	Age 75-84 Number (Percentage) N= 55	Age 85+ Number (Percentage) N=4
Delirium	0	0	4 (7.3%)	0
Depression	0	4 (3.3%)	3 (5.5%)	0

2.6.8.8. Immunological events

In the overall population (ie, all patients with B-NHL from Studies 1625 and 1333), the incidence of treatment-emergent ADA was 1.5% (6/400).

2.6.8.9. Safety related to drug-drug interactions and other interactions

Elevation of cytokines due to CRS may suppress CYP450 enzyme activities. The highest risk is during cycle 1 in patients who are receiving concomitant CYP450 substrates, particularly those with a narrow therapeutic index.

2.6.8.10. Discontinuation due to adverse events

Follicular lymphoma

Treatment-Emergent Adverse Events Leading to Dose Delay/Interruption

Per the protocol, odronextamab was held until resolution of any TEAE of grade ≥3. Overall, 129/153 (84.3%) patients had TEAEs leading to dose delay/interruptions. TEAEs occurring in ≥5% of patients that led to dose delay/interruption were COVID 19, CMV infection reactivation, Pneumonia, upper respiratory tract infection, CRS, IRR, Neutrophil count decreased, Neutropenia, and Pyrexia.

Treatment-Emergent Adverse Events Leading to Treatment Discontinuation

Overall, 21/153 (13.7%) patients experienced TEAEs resulting in treatment discontinuation. TEAEs occurring in ≥2 patients that led to treatment discontinuation were COVID 19, COVID 19 pneumonia, Pneumonia, IRR, Anaemia, and Myelodysplastic syndrome.

11/153(7.2%) patients had treatment-related TEAEs that led to treatment discontinuation. The only treatment-related TEAE that led to treatment discontinuation occurring in ≥2 patients was IRR.

DLBCL

Treatment-Emergent Adverse Events Leading to Dose Delay/Interruption

Per the protocol, odronextamab was held until resolution of any TEAE of grade ≥3. Overall, 146/219 (66.7%) patients experienced TEAEs leading to dose delays/interruptions. TEAEs occurring in ≥5% of patients that led to dose delay/interruption were, by PT, COVID 19, Pneumonia, CRS, Pyrexia, Neutropenia, and IRR

Treatment-Emergent Adverse Events Leading to Treatment Discontinuation

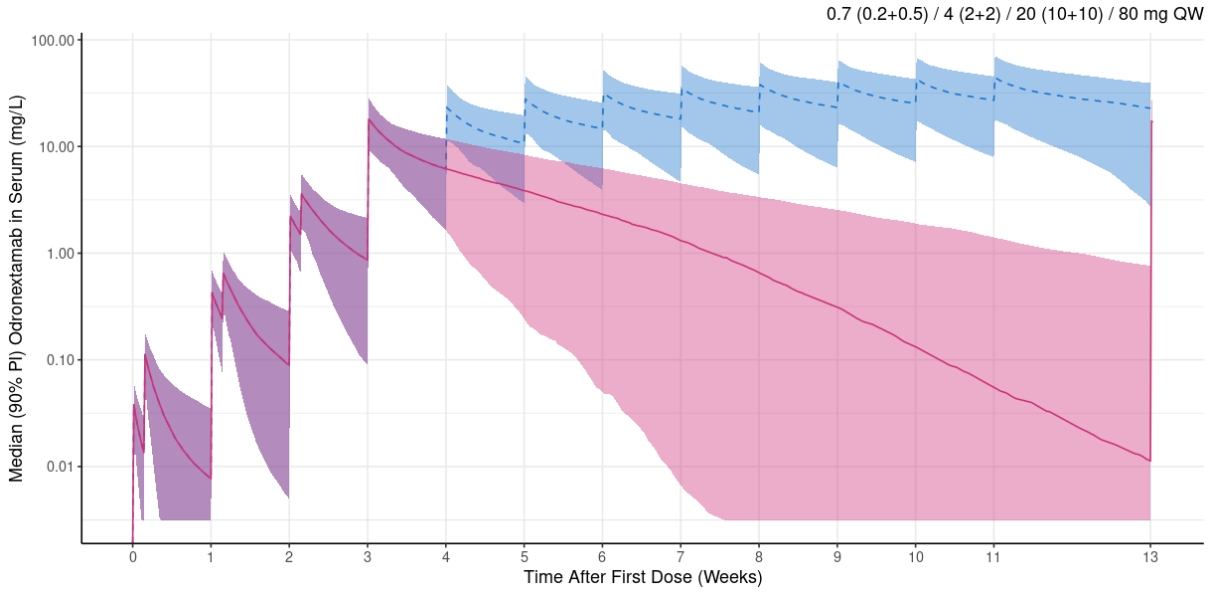
Overall, 30/219 (13.7%) patients with DLBCL experienced TEAEs resulting in treatment discontinuation. TEAEs occurring in ≥2 patients that led to treatment discontinuation were, by PT, COVID 19, Pneumonia, Pulmonary tuberculosis, Pneumocystis jirovecii pneumonia, Encephalopathy, and CRS.

21/219 (9.5%) patients had treatment-related TEAEs that led to treatment discontinuation. The treatment-related TEAEs that led to treatment discontinuation occurring in ≥2 patients were Encephalopathy, CRS, Pneumonia, COVID-19 and Pneumocystis jirovecii pneumonia

2.6.8.11. Dose resumption algorithm

Rationale of the dose resumption algorithm was initially based on predicted odronextamab concentration-time profiles (Figure 4) with or without a dose delay and then verified by clinical CRS data collected from Study 1333 and Study 1625 in patients received 0.7/4/20 mg step-up doses. The observed clinical CRS data used for supporting the proposed Treatment Resumption Guidelines are provided below. If the interruption was greater than 10 weeks, it is proposed to restart at the initial 0.2 mg dose from a conservative perspective, as the concentration could be below the predicted trough concentration of week 1.

Figure 19: Median and 90% Prediction Interval Simulated Odronextamab Concentration Time Profile After Administration of 80 mg as Target Dose (Blue Curve and 10-week Delay in Red).



Blue dashed lines are median and blue shaded areas are 90% predicted intervals of the nominal simulations. Red solid lines are median and red shaded areas are 90% predicted intervals of the simulations with a delayed dose.

Table 73: **Summary of CRS Incidence in Patients Restarting Therapy After Dose Delay or Following Proposed Regimens Without Dose Delay per Protocol**

Cycle	Last Dose Administered before Current Dose	Time from Last Dose Administered to the Current Dose	Number (%) of Dosing Events				
			# of all Dosing Events	No CRS	G1 CRS	G2 CRS	G3 CRS
2 to 4	80 mg QW for patients with r/r FL	Less than 11 days	371	362 (97.6%)	9 (2.4%)	0	0
		11 to 14 days	43	42 (97.7%)	1 (2.3%)	0	0
		15 to 28 days	23	22 (95.7%)	1 (4.3%)	0	0
		29 to 42 days	6	6 (100.0%)	0	0	0
		43 to 49 days	1	1 (100.0%)	0	0	0
		50 to 56 days	1	1 (100.0%)	0	0	0
		57 to 70 days	0	0	0	0	0
		More than 70 days	0	0	0	0	0
	160 mg QW for patients with r/r DLBCL	Less than 11 days	493	486 (98.6%)	5 (1.0%)	1 (0.2%)	1 (0.2%)
		11 to 14 days	59	58 (98.3%)	1 (1.7%)	0	0
		15 to 28 days	13	13 (100.0%)	0	0	0
		29 to 42 days	6	6 (100.0%)	0	0	0
		43 to 49 days	0	0	0	0	0
		50 to 56 days	0	0	0	0	0
		57 to 70 days	0	0	0	0	0
		More than 70 days	1	1 (100.0%)	0	0	0

2.6.8.12. Post marketing experience

N/A

2.6.9. Discussion on clinical safety

The main safety database comprises 146 patients with previously treated FL, exposed for a median of 31 weeks; and 201 previously treated patients with DLBCL, exposed for a median of 14 weeks. Updated numbers as per data cut of 19 Sep 2023 for Study 1333 and 20 October 2023 for Study 1625 are 153 treated FL and 219 DLBCL. Such size of the safety database would suffice for the sought CMA.

Overall, there is a considerable burden of adverse effects with odronextamab treatment. Approximately 80-85% of patients reported a grade ≥3 TEAE; approximately 65% (R/R DLBCL) to 85% (R/R FL) of patients required a dose interruption at some time. However, most patients managed to stay on odronextamab treatment, with a relatively modest 13.7% withdrawing from treatment due to an AE.

Adverse Events of Special Interest: CRS and IRR

The study program is characterised by two phases, interrupted by a partial Clinical Hold imposed by the FDA. During this, the sponsor revised the step-up dosing regimen to mitigate the risk of CRS, in addition to other mitigation measures including enhanced premedication and guidance on earlier intervention with tocilizumab for low grade CRS (i.e. tocilizumab use for patients with grade 1 CRS of fever lasting >24 hours and for all patients with grade ≥2 CRS).

There was an approximately 8-month interval between the last patient being enrolled in the 1/20 regimen and the first patient being enrolled in the slower ramp up with the 0.7/4/20 regimen (for details on these treatment regimens, see above under "dosing regimen and schedule".

The difference between these regimens in terms of total exposure is relatively minor. Nonetheless, the slower ramp up results in a reduction of grade ≥3 CRS. However, given it is not possible to disentangle between the implemented risk mitigation measures in their contribution to the reduced risk on grade ≥3 CRS, the modified guidance on use of tocilizumab and IV corticosteroids should be regarded as an integral part of this CRS risk minimization strategy.

In FL this reduction is from 5.3-1.4%, whereas in DLBCL, it is from 6.9-1.0%. The rates of CRS with the 0.7/4/20 regimen that is proposed for approval, is acceptable and not higher than what has been observed with previous products in the class. There were no fatal cases of CRS. As of the cutoff of 20 Oct 2023 for Study 1625 and 19 Sept 2023 for Study 1333 a total of 197 patients with FL and DLBCL indication have been treated with the 0.7/4/20 mg step up regimen. A total of 54.4% of patients experienced CRS of any grade (grade 1 in 39.6%, grade 2 in 13.7%, grade 3 in 1.0% and no grade 4 or 5 CRS). Management of CRS, in accordance with the amended study protocols, is described in the SmPC. Including also recommendations in case of refractoriness of CRS to tocilizumab, in line with other approved T-cell engagers, including bispecific antibodies.

As there was an increase in steroid pre-medication in the modified set-up regimen the applicant performed a safety related investigation of any potential increase in steroid-related side effects. No increase in hypertension, Grade>3 infection or gastrointestinal bleeding following the revised set-up regimen. There was an increase in hyperglycaemia in the time frame: from the initial dose through the first full dose, including the duration prior to second full dose, these hyperglycaemia episodes were mostly Grade 1 and 2.

In line with the other approved products of the same class it is stated in the SmPC section 4.4 that all patients should be monitored for signs and symptoms of potential CRS during and following odronextamab administration. Additionally, there are recommendations for patients to remain within

proximity of a qualified healthcare facility for at least 24 hours after administration of each dose within the odronextamab step-up dosing regimen and the first full dose, and to seek immediate medical attention should signs or symptoms of CRS occur.

Some manifestations of IRR may be clinically indistinguishable from manifestations of CRS (e.g. fever, hypoxia and hypotension). In studies 1625 and 1333, an IRR was defined as any AE that occurs during the infusion, or within 2 hours after completion of the infusion; CRS was defined as an event occurring 6 or more hours from the start of the infusion or more than 2 hours after completion of the infusion. This time cutoff value is however not a well-established and validated criterion and is different compared with other products from the same class.

Although investigators were allowed to report CRS regardless of time of onset at their discretion, it cannot be excluded that the CRS/IRR definitions have influenced the CRS/IRR adverse event reporting/grading in these pivotal studies. To inform physicians on how the frequency of CRS and IRR was defined and on the potential of bias, a general footnote is included in 4.8. It does not, however, specify the time restrictions in the CRS/IRR definition to avoid a delay in managing early CRS events.

Predicted odronextamab concentration-time profiles supported by clinical CRS data were used to develop an algorithm for dosing when re-starting after a dose delay (Table 3 in SmPC section 4.2). In patients that have a dose delay after achieving the target dose, a delay of 7-10 weeks mandates restarting at 10 mg, whereas an interruption of more than 10 weeks mandates a restart at the initial 0.2mg dose.

Concerning the risk of serious or fatal infections

The risk of serious or fatal infection is a major concern with products of this class when treating haematological malignancies.

At the time of data cut of 19 Sep 2023 for Study 1333 and 20 October 2023 for Study 1625, 9/153 (5.9%) of FL patients died from Covid-19, and 7/153 (4.6%) died from other infections, including systemic mycosis, PML and toxoplasma.

In DLBCL, 8/219 (3.7%) of patients died from Covid-19, and another 5.9% from other infections, including CMV and P Jirovecii.

The high proportion of infectious deaths being due to Covid-19 is evident also in the updated outcomes of the 1625 study (42% in DLBCL and 69% in FL).

Interpreting infectious death rates in single arm trials for haematological malignancies is generally challenging, and more so when these were conducted during the Covid-19 pandemic. To contextualise rates of severe infections, the applicant conducted a US claims data analysis in the Optum database to estimate exposure adjusted incidence rates of hospitalised infections in real-world patients with FL and DLBCL who received 3L+ standard of care treatment.

Data captured from 1 Oct 2015 (when ICD-10 codes for FL and DLBCL became effective) through 31 Mar 2023, were utilised. Rates of COVID-19 infections were calculated starting 1 Jan 2020. Infection events were ascertained using ICD-10 codes. Due to the absence of severity grading in claims data, grade ≥3 events were contextualised by estimating hospitalised events, that is, an infection diagnosis associated with an inpatient medical claim in any position.

Further, because only month/year of death was available in the data, without attribution of cause of death, fatal infection events were operationalised based on death that occurred during the same or following calendar month of a hospitalised infection.

The resulting exposure-adjusted incidence rate of hospitalisation for infection, or for fatal infections, were not higher in the Ordspono experience compared to what was found in this RWE source.

There is no clustering of non-covid infectious deaths, in relation to the initiation of Ordspono.

Overall, this contextualisation serves to alleviate concerns that rates of fatal infection in the 1625 study represents an outlying experience compared to FL and DLBCL treatment in the same era outside this study.

However, residual uncertainty about the impact of treatment on OS is intrinsic to the single arm design of the pivotal study. This highlights the importance of delivering interpretable OS data in the confirmatory studies (R1979-HM-2299 and R1979-ONC-22102) related to a CMA for FL and DLBCL.

On other safety aspects

The mechanism of action for cytopenias encountered with odronextamab or with any CD20xCD3 bispecific antibody is poorly understood. One possible mechanism is cytokine mediated suppression of hematopoiesis by regulating the growth and differentiation of precursor cells in the marrow. The frequency of grade 3/4 decreases in Hb (15.8%), TPK (12.3%) and neutrophils (44.5%) suggest adverse drug reactions. The Applicant has therefore included dedicated guidance on dose modifications for neutropenia and thrombocytopenia in Table 6 of section 4.2 of the SmPC.

There were 8 cases of febrile neutropenia as of the latest updated data cut, 8/372 (2.2%). In 4 patients febrile neutropenia events were associated with an infection. Febrile neutropenia is a life-threatening condition and a causal relation to odronextamab is plausible. To mitigate the risk for the potential life-threatening AE of febrile neutropenia in patients treated with odronextamab, there is dedicated wording on Febrile neutropenia in the subsection of Serious infection in section 4.4 of the SmPC. Febrile neutropenia is further listed in the Table 7 of section 4.8 with a frequency of common.

In total, 10/153 (6.5%) patients with FL experienced grade 3 neurological toxicity events and 16/219 (7.3%) patients with DLBCL experienced grade 3 or 4 neurological toxicity events. No patient experienced a grade 5 event. Additionally, events representing neurotoxicity such as confusion, delirium, and aphasia are considered to be part of ICANS where cytokines may be implicated in the pathophysiology. Although ICANS was only reported in 0.3% (1 patient), it is noted that the study protocols (Study 1333 and Study 1625) started before the consensus grading of ICANS (using the immune effector cell-associated encephalopathy score (ICE score) was published in 2019 and that the protocols were not amended following this. As the ICE scores depend on assessment of patient status and behaviour during an event, it is not possible to re-evaluate cases of neurotoxicity using ASTCT grading, and thus the correct incidence of ICANS is not possible to derive. In the absence of a dedicated diagnostical procedure for ICANS, the association of neurologic events like confusion, delirium, encephalopathy and aphasia as part of ICANS are subjected to large uncertainty in a retrospective assessment.

Since, ICANS is a known AE that may follow T-cell engager therapy and, although in low frequency, 'Neurological toxicity including ICANS' is listed as important identified risk among the safety concerns in RMP v1.2 and further included in SmPC section 4.4 with text also addressing monitoring and management. The lack of systematic assessment of ICANS with ICE scoring in the clinical studies (1333 and 1625) is noted with text under the table in section 4.8. Although the ICE scoring is not relevant for all neurotoxicity but only for ICANS, the Applicant has included the ICE scoring and associated management of ICANS (with and without a concurrent CRS) in the SmPC for future applications according to current clinical guidelines. This is in line with other recently approved T-cell engaging products.

TLS is another side effect that has been associated with this class of drugs. Two out of 372 patients (0.5%) experienced TLS on the 1/20 step-up regimen, while no patient treated with the recommended 0.7/4/20 mg step-up regimen experienced TLS and there were no fatal cases. TLS is listed as an

"uncommon" AE in section 4.8. The severity of the condition and given the small safety database, the applicant has provided language on TLS in 4.4 as also present for all the other approved BiTEs.

At data cut (20 Oct 2023 for Study 1625 and 19 Sep 2023 for Study 1333), there were 12 patients with pneumonitis/ILD the majority of which had a concurrent infection (7/12). Although there may be difficulties to distinguish pneumonitis/ILD from an infection at least 3/12 had no infection. And even though the biologic mechanism linking this product and ILD is currently not understood, it can be noted that interstitial lung disease (including fatal cases) is listed in section 4.8 for the anti-CD20 monoclonal antibody rituximab and has further been reported in the literature. Therefore ILD is listed among the ADR in 4.8 and given the potential severity of pneumonitis/ILD a warning is included in 4.4, stating pneumonitis/ILD as a differential diagnosis to pulmonary infections in case of respiratory symptoms without any causative pathogen.

There were 2 cases of fatal hemophagocytic lymphohistiocytosis (one in FL and one in DLBCL). It is acknowledged that HLH may be caused by among others the disease itself or EBV infection (which in turn could be triggered by drugs or the disease). HLH is considered a potential risk following T-cell engager therapy, while at present the causal relation to odronextamab is unclear, therefore inclusion in 4.4 or 4.8 is at present not necessary, while it is considered to add HLH as risk that should be followed in the PSUR without inclusion to the RMP.

Six patients fulfilled the laboratory criteria of Hy's law, 5 of these were found during set-up phase and could be cytokine mediated. CRS can be associated with hyperbilirubinemia, therefore a causal relationship between odronextamab treatment and Bilirubin increased is at least a reasonable possibility. Although it is not further suspected that odronextamab may exhibit specific hepatotoxicity, blood bilirubin increased (Frequency Common) is listed among the ADRs in section 4.8 of the SmPC.

A number of 20 overdose events have been reported in 9 patients (9/372; 2.4%), which is considered not negligible. The Applicant therefore included "Risk of overdose due to medication errors" as important potential risk in the RMP.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

Additional safety data needed in the context of a conditional MA

The lack of safety data from randomised controlled clinical trials will be addressed through the SOBs agreed.

2.6.10. Conclusions on the clinical safety

The adverse effect profile of odronextamab is manageable and as expected for this drug class. However data as derive from a single arm trial cannot be considered comprehensive. Therefore, there is remaining uncertainty on the precise risks associated with treatment and data are considered non-comprehensive with respect to safety. Confirmation of the safety profile through randomised controlled trials is required.

The CHMP considers the following measures necessary to address the missing safety data in the context of a conditional MA.

- In order to provide further evidence of efficacy and safety of odronextamab in relapsed or refractory follicular lymphoma, the MAH will provide results from study R1979 ONC 22102, a phase 3, open label, randomised trial to compare the efficacy and safety of odronextamab in combination with lenalidomide versus rituximab in combination with lenalidomide in relapsed or refractory participants with follicular lymphoma and marginal zone lymphoma.

- In order to provide further evidence of efficacy and safety of odronextamab in relapsed or refractory diffuse large B cell lymphoma, the MAH will provide results from study R1979 HM 2299, a phase 3, randomised, open-label trial evaluating the efficacy and safety of odronextamab versus Standard of Care therapy in participants with relapsed or refractory aggressive B cell non-Hodgkin Lymphoma.

The CHMP also considers the following measures necessary to address issues related to safety:

- A Patient Card containing the following key messages:

Description of the main signs or 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 other than in addition to the prescriber (e.g., emergency healthcare professionals); Prompts to enter contact details of the physician

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.

These conditions fully reflect the advice received from the PRAC.

2.7. Risk Management Plan

2.7.1. Safety concerns

Table 74 Summary of Safety Concerns

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

2.7.2. Pharmacovigilance plan

Table 75: Planned and on-going post-authorisation efficacy studies that are conditions of the marketing authorisation or that are specific obligations.

Study Status	Objectives	Efficacy Uncertainties Addressed	Milestones	Due Dates
Efficacy studies which are conditions of the marketing authorisation				
Not applicable				
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): 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 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 **Safety concerns addressed:** **CRS; Serious Infections, Neurologic toxicity including ICANS** **Long term safety**	Protocol Interim reports Final study report	31 Jul 2023 None Nov 2028
R1979-ONC-22102 (Olympia-5): 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. 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 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 FL and MZL) as measured by PFS per independent central review.	To further confirm clinical efficacy and safety of odronextamab in R/R FL **Safety concerns addressed:** **CRS; Serious Infections, Neurologic toxicity including ICANS** **Long term safety**	Protocol Interim reports Final study report for FL	31 Jul 2023 Sept 2031

2.7.3. Risk minimisation measures

Table 76 Additional Risk Minimisation Measures

Additional Risk Minimisation Activity 1 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. 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. 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.

2.7.4. Conclusion

The CHMP considers that the risk management plan version 1.2 is acceptable.

The Applicant is reminded that in case of a Positive Opinion, the body of the RMP and Annexes 4 and 6 (as applicable) will be published on the EMA website at the time of the EPAR publication, so considerations should be given on the retention/removal of Personal Data (PD) and identification of Commercially Confidential Information (CCI) in any updated RMP submitted throughout this procedure.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The international birth date (IBD) is the EU birth date (EBD). The new EURD list entry will therefore use the EBD to determine the forthcoming Data Lock Points.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Labelling exemptions

A request to omit certain particulars from the labelling as per Art. 63(3) of Directive 2001/83/EC has been submitted by the applicant and has been found acceptable by the QRD Group for the following reasons:

The group has accepted the use of minimum particulars for Ordspono 320mg (20mL vial) and the use of a blank piece of paper (package spacer) within the box for stability purposes (in all strengths). It was also agreed to include the text: "Package Spacer These pages are intentionally left blank." in the page spacer, and that this text should be added to the PI annexes (at the end of Annex IIIA).

2.9.3. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Ordspono (odronextamab) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not

contained in any medicinal product authorised in the EU.

Therefore the summary of product characteristics and the package leaflet include a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

- *Ordspono as monotherapy is indicated for the treatment of adult patients with relapsed or refractory follicular lymphoma (r/r FL) after two or more lines of systemic therapy.*
- *Ordspono as monotherapy is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (r/r DLBCL), after two or more lines of systemic therapy.*

3.1.2. Available therapies and unmet medical need

Follicular Lymphoma (FL)

Patients with FL who have received ≥2 prior therapies have a poor prognosis, with a median PFS ranging from 1 to 1.1 years for third-line patients decreasing to 0.5 years for sixth-line patients with a corresponding median OS of 4.8 to 8.8 years and 1.9 years, respectively (Alperovich, 2016, Batlevi, 2020, Rivas-Delgado, 2019). For patients in later treatment lines, there is currently no treatment considered standard of care, although several options are available.

The combination of lenalidomide with rituximab, and obinutuzumab with bendamustine are the only available therapies that have full approvals in the EU, for r/r FL in second line. In the third line setting, available treatment options include CAR-T products, CD20xCD3 bispecific antibody (mosunetuzumab), PI3K inhibitor therapy, BTK inhibition, and radioimmunotherapy.

CAR-T products have been recently approved in r/r FL $\geq$ 2 L (Kymriah) and $\geq$ 3 L (Yescarta). Yescarta has showed efficacy of 91% ORR, 77% CR, and 38.6 months DoR. However, CAR-T products are associated with CRS and neurotoxicity. Further, CAR-T therapy is not feasible in all circumstances due to patient comorbidities and manufacturing delays.

A recent conditional approval for the treatment of r/r FL after 2 prior lines of systemic therapy is the one of mosunetuzumab, a CD20xCD3 bispecific antibody which demonstrated an ORR of 80%, CR of 60%, and median DoR of 22.8 months.

PI3K inhibitors (idelalisib and duvelisib) are approved in r/r FL $\geq$ 2L. The PI3K inhibitors in the use for treating patients with FL yield CR rates between 1% to 8% and the utility of PI3K inhibitors for patients with FL is limited due to safety issues.

In addition, the BTK inhibitor Brukinsa has been recently approved in EU, in combination with obinutuzumab, for the treatment of adult patients with r/r FL who have received at least two prior systemic therapies.

An unmet medical need remains, as disease in the late line setting is debilitating and incurable.

Diffuse Large B-Cell Lymphoma (DLBCL)

Patients with **r/r DLBCL** after 2 or more lines of therapy have a poor prognosis. CR-rates between approximately 30-50% have been reported from different treatment options. A median OS of approximately 6 months in the third- or later lines setting of r/r DLBCL has been observed (Radford, 2019). For patients with r/r DLBCL after 2 or more lines of therapy, three CAR-T products (Yescarta, Breyanzi and Kymriah) have full marketing approvals in the EU, showing ORRs of approximately 55-70% in the 3L+ r/r DLBCL setting. However, as stated above, CAR-T therapies are also associated with adverse events for CRS and neurotoxicity, and not feasible or accessible in all circumstances.

Loncastuximab, a CD19-directed antibody drug conjugate, has a conditional approval in the EU for r/r DLBCL after 2 or more lines of therapy, with ORR of 48%, CR of 25%, and median DoR of 13 months.

Recently, the CD20/CD3 bispecific antibodies glofitamab (ORR 50%, CR 35%, mDoR 14 months) and epcoritamab (ORR 62%, CR 39%, mDoR 16 months) were granted a conditional marketing authorisation in the EU. Confirmatory studies are awaited.

Although recently approved therapies have improved outcome measures for relapsed or refractory DLBCL patients, there remains an unmet medical need as disease in this setting is debilitating and incurable.

3.1.3. Main clinical studies

Study 1625 is an ongoing, open-label, single-arm, multi-center, phase 2 study of odronextamab in patients with 5 disease-specific B-NHL cohorts: FL, DLBCL, MCL, MZL and other B-NHL (containing aggressive B-NHL subtypes not included in the other 4 cohorts) that have relapsed after or are refractory to prior systemic therapy.

Key eligibility criteria unique for **FL** were relapsed or refractory FL grade 1-3a (WHO 2017) after at least 2 prior lines of therapy.

Key eligibility criteria unique for **DLBCL** were relapsed or refractory DLBCL after at least 2 prior lines of therapy. Patients with de novo DLBCL or transformed DLBCL, from FL or CLL could, be enrolled.

Odronextamab was administered IV, first in 4 cycles (each cycle was 21-day) and then in a maintenance phase with Q2W dosing. If a patient had maintained CR for 9 months, then odronextamab was to be administered every 4 weeks at the same dose.

Selected RP2D regimens were:

- 80 mg QW/160 mg Q2W followed by 160 mg Q4W for **FL**
- 160 mg QW/320 mg Q2W followed by 320 mg Q4W for **DLBCL**

The sponsor revised the step-up dosing regimen to mitigate the risk of CRS, resulting in the revised 0.7/4/20 mg step-up regimen, which provides a somewhat slower ramp-up than the initial 1/20 mg step-up.

The primary endpoint was ORR according to the Lugano Classification (Cheson, 2014) as assessed by independent central review for each of the five disease-specific cohorts in study 1625. Secondary endpoints included CR, DoR, PFS and OS.

128 patients with r/r **FL** were efficacy evaluable (defined as patients with or who had the opportunity for response assessment at 12 weeks); 60 patients received the 0.7/4/20 regime and 68 patients received the 1/20 regimen.

127 patients with r/r **DLBCL** were efficacy evaluable (defined as patients with or who had opportunity for response assessment at 12 weeks); 67 patients received the 1/20 mg regimen and 60 patients received the 0.7/4/20 mg regimen.

Moreover, the exploratory study 1333 included 60 patients with DLBCL who were relapsed or refractory to CAR-T therapy.

3.2. Favourable effects

In FL and as of updated DCO 20 Oct 2023, ORR (primary endpoint, n=128) was 80.5% (95% CI: 72.5%, 86.9%), with a CR in 73.4% (95% CI: 64.9%, 80.9%) of the patients. The lower bound of the 95% CI for ORR exceeded the 49% rate prespecified ORR in the SAP.

The median DoR (n=128) was 22.6 months (95% CI 17.7, NE).

Regarding DLBCL, in 1625 study, as of the updated DCO 20 Oct 2023, ORR (primary endpoint, n=127) was 52% (95% CI 43, 61), with a CR rate in 31.5% (95% CI 24, 40) of the patients. The lower bound of the 95% CI for ORR exceeded the 35% rate prespecified ORR in the SAP.

The median DoR (n=127) was 10.5 months (95% CI 5.0 to 24.8).

In a subset of 60 patients in the 1333 study that had previously received CAR-T therapy, ORR was 48.3% (95% CI 35.2% to 61.6%) and CR of 31.7% (95% CI 20.3% to 45.0%). The KM estimated mDoR was 14.8 months (95% CI 2.8, NE).

3.3. Uncertainties and limitations about favourable effects

Data derive from single arm studies of an exploratory nature, therefore, OR/CR rates may be subject to selection bias. Moreover, the impact of odronextamab on time-dependent endpoint including PFS and OS cannot be isolated.

Activity estimates for "high-grade B-cell lymphoma" (HGBL) estimates (ORR 17% in triple-hit patients n=6 and ORR 0% in double-hit patients n=5) are low and uncertain due to a limited sample.

The applicant will provide confirmatory data from randomised controlled studies; study R1979 ONC 22102, a phase 3, open label, randomised trial to compare the efficacy and safety of odronextamab in combination with lenalidomide versus rituximab in combination with lenalidomide in relapsed or refractory participants with follicular lymphoma and marginal zone lymphoma. And study R1979 HM 2299, a phase 3, randomised, open-label trial evaluating the efficacy and safety of odronextamab versus Standard of Care therapy in participants with relapsed or refractory aggressive B cell non-Hodgkin Lymphoma (see RMP and Annex II).

3.4. Unfavourable effects

The initial main safety database comprises 146 patients with previously treated FL, exposed for a median of 31 weeks; and 201 previously treated patients with DLBCL, exposed for a median of 14 weeks. After data cut of 19 Sep 2023 for Study 1333 and 20 October 2023 for Study 1625 there were 153 FL patients and 219 DLBCL patients in the safety data base.

Approximately 80-85% of patients reported a grade ≥3 TEAE; approximately 65% (R/R DLBCL) to 85% (R/R FL) of patients required a dose interruption at some time. However, most patients managed to stay on odronextamab treatment, with 13.7% withdrawing from treatment due to an AE.

The most common adverse reactions were cytokine release syndrome (54%), neutropenia (41%), pyrexia (39%), anaemia (38%), thrombocytopenia (27%), diarrhoea (24%), and COVID-19 (22%). The most common severe (NCI CTCAE Grade ≥ 3) adverse reactions were neutropenia (34%), anaemia (19%), thrombocytopenia (13%), lymphopenia (12%), pneumonia (10%), leukopenia (9%), COVID-19 (8%), hypokalaemia (6%), and hyperglycaemia (5%).

Two different step-up regimens were used during development. The step-up regimen was modified to mitigate the risk of CRS after 175 patients (74 with r/r FL and 101 with r/r DLBCL) were enrolled. Data for CRS and IRR are reported in 197 patients (79 with r/r FL and 118 with r/r DLBCL) who received the recommended step-up dosing regimen. In patients with r/r FL or r/r DLBCL (combined) treated with the recommended step-up dosing regimen, 24% experienced CRS after Cycle 1, Day 1 or 2, 29% experienced CRS after Cycle 1, Day 8 or 9, and 26% experienced CRS after Cycle 1, Day 15 or 16. From Cycle 2 on, 22% of patients experienced CRS. From Cycle 3 on, 4.6% of patients experienced CRS. With continued Ordspono dosing, the incidence and severity of CRS decreased. The median time to onset of CRS from the end of infusion across all doses in the combined group of patients treated with the recommended step-up dosing regimen was 19.8 hours (range: -3.4 hours to 9 days); 99% of CRS events resolved, and the median duration of CRS was 2 days (range: 1 to 10 days).

n FL, 5.2% of patients died within 90 days of last dose of odronextamab from Covid-19, and another 3.3% died within 90 days of last dose of odronextamab from other infections, including PML. In DLBCL, 3.7% of patients died within 90 days of last dose of odronextamab from Covid-19, and another 5.0% from other infections, including CMV and P Jirovecii. There were 5 cases of pneumonitis. In the FL Grade 1-3a 80mg QW group, one Grade 3 in the 1/20 step-up scheme and two Grade 3 + one Grade 4 in the 0.7/4/20 step-up. Additionally, in the DLBCL 160mg QW group there are two cases of ILD (interstitial lung disease) among the TEAE leading to death.

Among 372 patients with r/r FL or r/r DLBCL, the most frequent neurologic toxicities of any grade were headache (13%), dizziness (8%), anxiety (4.3%) and confusional state (3.5%), and encephalopathy (3%). Grade 3 or 4 neurologic adverse reactions occurred in 7% of patients, a Grade 2 ICANS was reported.

TLS was reported in 0.5% of patients (N=2); both events were Grade 3; onset was on Day 2 and Day 7, both resolved within 2 days.

3.5. Uncertainties and limitations about unfavourable effects

Overall, the main uncertainties on unfavourable effects relate to the lack of a randomised control arm in the studies that have been performed. A particular concern is the risk of serious or fatal infections. The assessment of the impact of odronextamab treatment on this risk is further hampered by the fact that the pivotal trials were performed during the Covid-19 pandemic. The applicant has contextualised findings using real world evidence. This does not indicate outlying results. However, a further understanding of the burden of serious and fatal infection is necessary in the context of RCTs as SOBs for the CMA (see Recommendations and RMP).

In order to address the uncertainties arising from the lack of comparative data, the applicant will provide confirmatory data from randomised controlled studies; study R1979-ONC-22102, a phase 3, open label, randomised trial to compare the efficacy and safety of odronextamab in combination with lenalidomide versus rituximab in combination with lenalidomide in relapsed or refractory participants with follicular lymphoma and marginal zone lymphoma. And study R1979-HM-2299, a phase 3, randomised, open-label trial evaluating the efficacy and safety of odronextamab versus Standard of Care therapy in participants with relapsed or refractory aggressive B cell non-Hodgkin Lymphoma (see RMP and Annex II).

3.6. Effects Table

Table 77 Effects Table for odronextamab R1979 ONC-1625 study, in adult patients with relapsed or refractory follicular lymphoma (r/r FL) and relapsed or refractory diffuse large B cell lymphoma (r/r DLBCL) after at least 2 lines of systemic therapy. (Data cut-off for the Interim Analysis (FL)/Primary Analysis (DLBCL): 31 January 2023; Data cut-off for updated analyses FL and DLBCL: 20 Oct 2023)

Effect	Short Description	Unit	Treatment	Uncertainties/ Strength of evidence	Ref
Favourable Effects					
ORR by IRC (primary endpoint)	Objective response rate **FL:** ORR (CR+PR) **DLBCL:** ORR (CR+PR)	N (%) (95% CI)	103/128 (80.5 %) (72.5, 86.9%) 66/127 (52.0%) (42.9%,60.9%)	Unc: Exploratory, single-arm trial, limited sample size. Indication sought in two out of 5 five disease-specific cohorts in study 1625. First response assessment performed at week 12. SoE: Support from secondary endpoints. Support from study 1333 with a subset of 60 patients that had previously received CAR-T therapy, ORR was 48.3% (95% CI 35.2% to 61.6%), CR was 31.7% (95% CI 20.3% to 45.0%), and the mDoR was 14.8 months (95% CI 2.8, NE).	
CR by IRC (secondary endpoint)	Complete response **FL** **DLBCL**	N (%) (95% CI)	94/128 (73.4%) (64.9, 80.9%) 40/127 (31.5%) (23.5, 40.3%)	As above	
DoR by IRC (secondary endpoint)	Duration of response **FL** **DLBCL**	Months (95% CI)	22.6 (17.7, NE) 10.5 (5.0, 24.8)	Unc: Short follow-up	

Effect	Short Description	Unit	Treatment	Uncertainties/ Strength of evidence	Ref
DoCR by IRC (secondary endpoint)	Duration of complete response **FL** **DLBCL**	Months (95% CI)	 25.1 (20.5, NE) 17.9 (10.2, NE)	Unc: Short follow-up	
Unfavourable Effects					
Grade ≥3 TEAEs	Updated Combined Primary Pool (153 FL + 219 DLBCL) (N=372)	% (N)	**84.1%** (N=313)	Unc: Based on single arm studies with no comparator. Safety database is limited in size and follow-up.	Summary of Clinical Safety document
Serious TEAEs			**63.7%** (N=237)		
Fatal TEAEs			**13.4%** (N=50)		
TEAEs leading to discontinuation			**13.7%** (N=51)		
CRS	Updated FL+DLBCL Pool (0.7/4/20 step-up) (N=197)		**54.3%** (N=107)		
Neurotoxicity grade ≥3	Initial Combined Primary Pool (FL+DLBCL) (N=372)		**7.8%** (N=29)		
TLS			**0.5%** (N=2)		
Serious infections			**37.4%** (N=139)		
Fatal Infections			**8.6%** (N=32)		

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

There is an unmet need for patients with R/R FL and R/R DLBCL who have received ≥2 prior therapies, particularly for patients who are R/R to different classes of agents, as they are left with limited treatment options that may have challenging safety profiles.

Results from the single-arm Study 1625 are very encouraging, with 94/128 (73.4%) of FL and 40/127 (31.5%) of DLBCL patients achieving CR. Obtaining a CR, which is the disappearance of all measurable evidence of disease, is considered highly relevant for this population in need and indicates a clinically meaningful effect. Results from secondary endpoints, support the primary endpoint.

The size of the safety database is sufficient. Class related concerns include cytokine release syndrome (CRS), severe infections, immune effector cell-associated neurotoxicity syndrome (ICANS), infusion-related reactions (IRR) and tumour lysis syndrome (TLS). The evaluation of serious infections with odronextamab is hampered by the single arm design of the trials performed during the Covid-19 pandemic in risk groups for severe covid. Consequently Covid-related morbidity and mortality is notable. A contextualisation of rates of serious and fatal infections comparing to RWE has been provided which was reassuring. Remaining unclarities about incidence are anticipated to be clarified in the proposed confirmatory randomised controlled trials.

3.7.2. Balance of benefits and risks

Anticipated benefits outweigh risks, for the indications approved:

- *Ordspono as monotherapy is indicated for the treatment of adult patients with relapsed or refractory follicular lymphoma (r/r FL) after two or more lines of systemic therapy.*
- *Ordspono as monotherapy is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (r/r DLBCL), after two or more lines of systemic therapy*

Confirmatory trials have been designed as specific obligations in order to provide comparative comprehensive information on the impact of the treatment with Ordspono (see section 3.7.3) in the context of the CMA.

3.7.3. Additional considerations on the benefit-risk balance

As discussed, the single arm exploratory trial design introduces inherent limitations in the interpretation of the results - based on non-comparative data. Based on the above, the clinical data cannot be considered comprehensive.

Conditional marketing authorisation

As comprehensive data on the product are not available as discussed above, a conditional marketing authorisation was requested by the applicant in the initial submission.

The product falls within the scope of Article 14-a of Regulation (EC) No 726/2004 concerning conditional marketing authorisations, as it aims at the treatment of a seriously debilitating, life-threatening diseases – previously treated FL and DLBCL.

Furthermore, the CHMP considers that the product fulfils the requirements for a conditional marketing authorisation:

- **The benefit-risk balance is positive**

The benefit – risk balance is positive as discussed extensively in section 3 above.

- **It is likely that the applicant will be able to provide comprehensive data**

The Applicant proposes the below studies to be considered specific obligations of the CMA (see also Clinical Efficacy section).

Follicular lymphoma

Study R1979-ONC-22102 is a Phase 3, open label, randomized study to compare the efficacy and safety of odronextamab in combination with lenalidomide therapy versus rituximab in combination with lenalidomide (R2) therapy in participants with R/R FL and MZL in > 2 line. The primary endpoint of PFS is assessed by IRC. The final CSR is projected to be provided by September 2031.

DLBCL

Study R1979-HM-2299 is a Phase 3, randomized, open label study, evaluating efficacy and safety of odronextamab versus Standard of Care (SOC) salvage therapy followed by ASCT in participants with R/R aggressive B-cell non-Hodgkin lymphoma. The primary objective is EFS, in participants with odronextamab versus participants with SOC. The CSR will be submitted by November 2028.

- **Unmet medical needs will be addressed, as**

In line with Section 4.1.2 c) of the 'Guideline on the scientific application and the practical arrangements necessary to implement Commission Regulation (EC) No 507/2006 on the conditional marketing authorisation for medicinal products for human use falling within the scope of Regulation (EC) No 726/2004', when comparing the efficacy results of odronextamab to available therapies approved under a CMA for the same target population, being Minjuvi, Zynlonta, Columvi, and Tepkinly, odronextamab addresses the unmet medical need to a similar extent whereas the safety profile is in line with what is seen in this class of products.

In addition, the applicant has provided satisfactory evidence for major therapeutic advantages (MTA) over existing therapies (polatuzumab vedotin (+BR), CAR-T therapies and pixantrone) approved as a full marketing authorisation, see below detailed comparisons per product/ indication:

DLBCL – Discussion of the MTA of Ordspono vs products approved as full MA

CAR-T therapies: Breyanzi, Kymriah and Yescarta

As noted by the applicant, the MTA of odronextamab vs CAR-T is demonstrated on the basis that odronextamab is an off-the-shelf treatment option regardless of access to transplant/specialized CAR-T centres and has the potential to be less onerous on patients.

While ORR and CR rates are clinically meaningful for both odronextamab and the CAR-T products, these are higher for the latter. On the other hand, the risk of CRS is lower with odronextamab.

An MTA over Breyanzi, Kymriah and Yescarta is therefore agreed based on major contribution to patient care.

Polivy

The polatuzumab-BR arm of pivotal study GO29365 had 27.5% of patients with only 1 prior line of therapy and 75% were refractory to last line of therapy whereas all patients in the odronextamab r/r DLBCL studies had relapsed or were refractory to least two prior lines of systemic therapies at baseline and 86.6% of patients in Study 1625 were refractory to last line of therapy.

Despite these differences, response rates between polatuzumab-BR (ORR of 47.5% and CR of 40.0%) (Polivy [Summary of Product Characteristic], 2023) and odronextamab's Study 1625 [ORR: 52%, 95% CI: 43%, 61%; CR rate: 31.5%, 95% CI: 23%, 40%] were generally similar.

Moreover, in the 1333 study, the activity of odronextamab was shown in patients previously treated with CAR-T therapy. Such data are not available for Polivy.

The applicant stated that serious AEs [64.4% (29/45)], fatal TEAEs [20.0% (9/45)], and serious TEAEs of infections were reported among 28.9% of patients receiving polatuzumab-BR. Particularly, neutropenia [any grade: 60.0%, grade 3/4: 55.6%] was also reported for patients receiving

polatuzumab-BR (EMA, 2019 Polivy EPAR). Overall, odronextamab is associated with lower grade ≥3 neutropenia: 16.9% (37/219)] compared to polatuzumab-BR.

This difference is credible based on the different MoA of a CD20xCD3 antibody, and an ADC with a microtubule-targeting toxin in combination with a chemotherapy agent. Other differences in safety profile are also anticipated based on the known safety profile of microtubule disrupting agents like the toxin of Polivy, including irreversible peripheral neuropathy.

In accordance with previous evaluations of analogous comparison, the activity of odronextamab in patients having failed prior CAR-T therapy is noted. Moreover, substantially different AE profiles are anticipated based on different MoA's. In particular, microtubule-targeting toxins are known to cause peripheral neuropathy, which is a dose-limiting toxicity. Thus, an established potential to address a remaining UMN notwithstanding the approval of Polivy may be inferred.

DLBCL; Ordspono addressing UMN vs products approved as CMA

Minjuvi +lenalidomide *(CMA, addressing UMN to a similar extent)*

Despite patients receiving odronextamab having a substantially higher proportion characteristics associated with poor outcomes, response rates of odronextamab were generally similar in Study 1625 (ORR: 52%, 95% CI: 43%, 61%; CR rate: 31.5%, 95% CI: 23%, 40%) compared to tafasitamab in combination with lenalidomide combination therapy (ORR: 56.8% [46/81]; CR rate: 39.5% [32/81]) (Minjuvi [Summary of Product Characteristics], 2021). Serious TEAEs [43.8% (35/80)], and fatal TEAEs [5.0% (4/80)] were reported for patients receiving tafasitamab in combination with lenalidomide (EMA, 2021b, Minjuvi EPAR).

Based on cross-study comparisons, one may conclude that there are no differences in key efficacy and safety parameters indicative that odronextamab would address the UMN in DLBCL to a lesser degree than Minjuvi.

Zynlonta *(CMA, addressing UMN to the same extent)*

Response rates for odronextamab [ORR: 52%, 95% CI: 43%, 61%; CR rate: 31.5%, 95% CI: 23%, 40.0%] compared to loncastuximab tesirine [ORR: 48.3%; CR rate: 24.8% were roughly similar by cross study comparison. Serious TEAEs [39.3% (57/145)] fatal TEAEs [5.5% (8/145) were seen, (EMA, 2022c, Zynlonta EPAR). By cross study comparison, no substantial difference can be ascertained. Thus, there are no measured differences in key efficacy and safety parameters in this cross-study comparison indicative that odronextamab would address the UMN in DLBCL to a lesser degree than Minjuvi.

Tepkinly *(CMA, addressing UMN to a similar extent)*

Response outcomes were generally similar with overlapping 95% confidence intervals between epcoritamab's study GCT3013-01 (ORR: 61.9% [95% CI: 53.3%, 70.0%]; CR rate: 38.8% [95% CI: 30.7%, 47.5%]) and odronextamab's Study 1625 (ORR: 52% [95% CI: 43%, 61%]; CR rate: 31.5% [95% CI: 24%, 40%]). In the subgroup of epcoritamab patients in GCT3013-01 with prior CAR-T exposure (n=53), response rates were ORR 52.8% (95% CI: 38.6%, 66.7%) and CR rate 35.8% (95% CI: 23.1%, 50.2%). In Study 1333 of odronextamab (Oct 2023 DCO, N=60), 71.7% (43/60) of patients that had prior CAR-T exposure were refractory to CAR-T therapy and had a median of 3 prior lines of therapy (range: 2 to 9) with an ORR of 48.3% (95% CI: 35.2%, 61.6%) and CR rate of 33.3% (95% CI: 21.7%, 46.7%).

Serious TEAEs were reported in 58.8% (87/148) of patients and fatal TEAEs were reported in 7.4% (11/148) of patients receiving epcoritamab. For odronextamab serious TEAEs were reported among 62.1% (136/219) patients. 13.7% (30/219) experiencing a TEAE resulting in death. Notably, the

studies of epcoritamab and odronextamab were not temporally aligned, and the impact of Covid-19 may have been larger on the latter.

Given the similarity of the products, differences in ability to address UMN are not anticipated a priori. Altogether there are no robustly shown differences seen in these cross-study comparisons that would be indicative that the potential for odronextamab to address the UMN in its indication, is not similar to that of Tepkinly.

Glofitamab *(CMA, UMN to be addressed to a similar degree)*

Response outcomes in the CAR-T naïve population were generally similar between glofitamab [ORR: 52.4% (54/103); CR rate: 41.7% (43/103)] and odronextamab [ORR: 52%, 95% CI: 42.9%, 60.9%; CR rate: 31.5%, 95% CI: 23%, 40.0%].

In the post-CAR-T setting, which is an area of high unmet need, patients receiving glofitamab (ORR: 50.0%, CR rate: 35.2%) and odronextamab (ORR: 48.3%, CR rate: 33.3%) had similar response outcomes.

Serious TEAEs [48.7% (75/154)] and fatal TEAEs (5.8% [9/154]), were observed in patients receiving glofitamab. This is not substantially different from what was seen with odronextamab.

Given the similarity of mechanism of action between the two products, differences in ability to address UMN are not anticipated a priori. Altogether this cross-study comparison does not indicate that the potential for odronextamab to address the UMN in its indication, would be less that for glofitamab.

Follicular lymphoma; MTA of Ordspono vs products approved as full MA

Brukinsa + obinutuzumab

ORR and CR rates were higher for odronextamab monotherapy (ORR: 80.5% [95% CI: 72.5% to 86.9%]; CR: 73.4% [95% CI: 64.9%, 80.9%]) compared to zanubrutinib in combination with obinutuzumab (ORR: 69.0% [100/145], CR rate 39.3% [57/145]

Serious TEAEs (44.8% [64/143]) and fatal TEAEs (9.8% [14/143]) were reported among patients receiving zanubrutinib in combination with obinutuzumab. For odronextamab, serious TEAEs (66.0% [101/153]) and TEAEs resulting in death were reported among 13.1% (20/153) of patients.

This is a cross study comparison, wherefore differences in AE rates, as well as in ORR, are uncertain, and cannot be taken as facts. The difference in CR rates, however, is large enough to indicate an established potential for an MTA of odronextamab over zanubrutinib in combination with obinutuzumab.

Yescarta, Kymriah

The applicant states that a MTA of odronextamab is justified over CAR-T therapies by providing an accessible and off-the-shelf treatment option for all patients regardless of access to transplant/specialized CAR-T centres and has the potential to be less demanding on patients.

ORR and CR are roughly similar, whereas safety concerns are largely qualitatively similar.

An MTA over Breyanzi, Kymriah and Yescarta is relevant based on major contribution to patient care.

CD20-Directed Treatments

Several CD20-directed therapies are approved for the treatment of r/r FL including rituximab in combination with lenalidomide, obinutuzumab in combination with bendamustine.

Overall patients treated with odronextamab monotherapy have clearly higher response rates compared to each of the CD20-directed treatments and hence, odronextamab offers an MTA over CD20-directed therapies.

Revlimid + Rituximab

The AUGMENT study of lenalidomide in combination with rituximab did not include patients who were refractory to rituximab and as such results from this study are not generalizable to patients who are refractory to rituximab.

In the MAGNIFY study, patients with FL grade 1-3a had ORR of 72% (230/318) with confirmed or unconfirmed CR (CR/CRu) of 42% (134/318). For odronextamab, response rates in the overall efficacy analysis set of Study 1625 [ORR: 80.5%, CR rate: 73.4%]

In the FL safety population for lenalidomide in combination with rituximab, high-grade neutropenia was commonly reported (grade ≥3: 40.7%) (EMA, 2012a, Revlimid EPAR). The corresponding rate for odronextamab in FL was approximately 27%.

Based on cross study comparisons, one may confidently say that there is a greater depth of response with odronextamab in terms of higher rates of CR, which therefore has an established potential to address an UMN to a greater extent than lenalidomide/rituximab.

Gazyvaro in combination with Bendamustine

Among patients with FL who did not respond or who progressed during or up to 6 months after treatment with rituximab or a rituximab-containing regimen, best ORR and CR rate for obinutuzumab in combination with bendamustine was 79.7% and 15.7%, respectively.

For odronextamab, response rates in the efficacy analysis set of Study 1625 were ORR: 80.5%; CR rate: 73.4%

High grade neutropenia (grade ≥3: 35.8%) and thrombocytopenia (grade ≥3: 10.8%) was commonly reported for patients receiving obinutuzumab in combination with bendamustine.

Odronextamab has lower rates of high-grade neutropenia (grade ≥3: 28.1%) and thrombocytopenia (grade ≥3: 3.3%) compared to obinutuzumab in combination with bendamustine.

There is an MTA over obinituzumab+bendamustine based on a clearly higher CR rate, where the difference is large enough to be ascertained in a cross-study comparison.

Copiktra and Zydelig

Response rates and depth of responses of the PI3K class, (ORR: 40% and CR rate: 0%, (Copiktra); ORR: 55.6% and CR rate of 16.7%, (Zydelig), are way lower than those for odronextamab. Moreover, the class has also been associated with repeated observations of higher rates of death in RCTs which raises safety concerns with this class of treatments and hence the utility of duvelisib and idelalisib for patients with R/R FL is limited. Therefore, there is an MTA based on efficacy, since the activity of odronextamab is obviously higher, which can be concluded despite inherent limitations of cross-study comparisons.

Zevalin *(now withdrawn from the EU market)*

Patients receiving ibritumomab had an ORR of 74% and CR rate of 15% in patients with FL who were refractory to rituximab. In contrast to ibritumomab, odronextamab has demonstrated higher ORR (80.5%) and markedly higher CR rate (73.4%) in the efficacy analysis set as well as in the subgroup of patients who were refractory to anti-CD20 antibody [CR rate: 69.5% (66/95)]. Zevalin is a radiopharmaceutical, which may be hazardous in case of mishandling. It is agreed with the applicant

that there is an MTA based on convenience. Moreover, the CR rate is clearly higher for odronextamab notwithstanding cross study comparison. Therefore, there is an MTA also based on improvement in efficacy.

It should be noted that since Zevalin has not been available on the market since 2020, the "sunset clause" applied which resulted in the withdrawal of the MA in January 2024.

Pixuvri *(now withdrawn from the EU market)*

In the PIX 301 study pivotal for the Pixuvri approval, patients were required to have demonstrated sensitivity to prior anthracycline therapy. Patients receiving subsequently approved pixantrone monotherapy (n=70) had ORR of 37.1% (26/70) and CR rate of 11.4% (8/70) based on the 1999 International Working Group (IWG) criteria. In contrast, Study 1625 of odronextamab did not have any life expectancy or anthracycline sensitivity-related inclusion criteria with confirmed or unconfirmed Complete Response (CR) or Partial Response (PR) and have life expectancy of at least 3 months. Patients receiving odronextamab had higher ORR of 52% (66/127) and CR rate of 31.5% (40/127) based on the Lugano classification. Cardiac failure events related to pixantrone occurred in 8.8% (6/68) of patients treated with pixantrone in study PIX 301 whereas for odronextamab, approximately 2.3% (5/219) patients had MedDRA preferred terms of cardiac failure, cardiac failure acute and cardiac failure congestive. Notwithstanding cross study comparisons, this difference is plausible based on the known properties of anthracycline-like compounds. The difference in safety profile is measurable and plausible based on different MoA. There is an MTA based on improvement in safety.

It should be noted regardless that Pixuvri ceased to exist in the EU as the MAH did not to apply for a renewal of the MA.

Lunsumio (CMA, need to address UMN to the same extent)

Mosunetuzumab demonstrated similar ORR [80% (72/90), 95% CI: 70.3%, 87.7%] and CR rate [60% (54/90), 95% CI 49.1%, 70.2%], compared to odronextamab [ORR: 80.5%, 95% CI: 72.5%, 86.9%; CR rate: 73.4%, 95% CI 64.9%, 80.9%].

The safety profile of Lunsumio and odronextamab is, as may be anticipated given the similar mechanism of action, qualitatively similar. Reporting rates of serious AEs [52.3% (114/218)] and fatal AEs [1.8% (4/218)] are lower for Lunsumio. Overall survival at 12 months was 93% in the Lunsumio registrational dose cohort, whereas it is 86% in the odronextamab 1625 FL cohort. These figures are not robust enough for any conclusions of differences based on cross-study comparisons. Moreover, the odronextamab 1625 study was performed later, during the Covid-19 pandemic, whereas the Lunsumio studies were initiated approximately 6 months earlier and had a data cut off for the pivotal analysis almost one and a half years earlier than the odronextamab 1625 study. Also, there is no mechanistic reason to support real differences in efficacy.

Therefore, it is reasonable to state that the established potential to address the UMN in FL is similar for Lunsumio and odronextamab.

Conclusion for both indications DLBCL and FL

Thus, the applicant has demonstrated an MTA based on either efficacy, safety and major contribution to patient care over all relevant fully approved products. Moreover, the product is anticipated to address the UMN in DLBCL and FL to at least a similar degree as products approved under CMA.

Benefits to public health of the immediate availability will outweigh the risks inherent in the fact that additional data are still required.

Given the poor prognosis in r/r FL patients in > 3L therapy, it is agreed that the benefits to public health of immediate availability outweigh the risks inherent in the fact that additional data are still required.

Given the aggressive course of the disease with poor prognosis in r/r DLBCL patients in > 3L therapy, it is agreed that the benefits to public health of immediate availability would outweigh the risks inherent in the fact that additional data are still required.

3.8. Conclusions

The overall benefit/risk balance of Ordspono is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Ordspono is not similar to Yescarta, Kymriah, Polivy, Minjuvi, Columvi and Tepkinly in the treatment of **DLBCL** and not similar to Yescarta, Kymriah, Lunsumio and Gazyvaro in the treatment of **FL** within the meaning of Article 3 of Commission Regulation (EC) No 847/2000. See Appendix on Similarity.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Ordspono is favourable in the following indications:

- *Ordspono as monotherapy is indicated for the treatment of adult patients with relapsed or refractory follicular lymphoma (r/r FL) after two or more lines of systemic therapy.*
- *Ordspono as monotherapy is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (r/r DLBCL), after two or more lines of systemic therapy.*

The CHMP therefore recommends the granting of the conditional marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and

any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

The marketing authorisation holder (MAH) shall ensure that in each Member State where Ordspono is marketed, all patients/carers who are expected to use Ordspono have access to/are provided with the patient card which will inform and explain to patients the risks of cytokine release syndrome (CRS) and neurologic toxicity, including immune effector cell-associated neurotoxicity syndrome (ICANS). The patient card also includes important information for healthcare professionals treating the patient that the patient is receiving Ordspono which may cause CRS and neurologic toxicity, including ICANS.

The patient card shall contain the following key messages:

- A description of the key signs and symptoms of CRS and neurologic toxicity, including ICANS.
- A reminder that patients should be instructed to remain within proximity of a qualified healthcare facility for at least 24 hours after administration of each dose within the Ordspono step-up dosing regimen and after the first full dose.
- A description of when to seek urgent attention from a healthcare provider or seek emergency help, should signs and symptoms of CRS or neurologic toxicity, including ICANS present themselves
- The prescribing physician's contact details

- **Obligation to conduct post-authorisation measures**

Specific Obligation to complete post-authorisation measures for the conditional marketing authorisation

This being a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	**Due date**
In order to provide further evidence of efficacy and safety of odronextamab in relapsed or refractory **follicular lymphoma**, the MAH will provide results from study R1979-ONC-22102, a phase 3, open label, randomised trial to compare the efficacy and safety of odronextamab in combination with lenalidomide versus rituximab in combination with lenalidomide in relapsed or refractory participants with follicular lymphoma and marginal zone lymphoma.	Q3 2031
In order to provide further evidence of efficacy and safety of odronextamab in relapsed or refractory **diffuse large B cell lymphoma**, the MAH will provide results from study R1979-HM-2299, a phase 3, randomised, open-label trial evaluating the efficacy and safety of odronextamab versus Standard of Care therapy in participants with relapsed or refractory aggressive B cell non-Hodgkin Lymphoma.	Q4 2028

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable

New active substance status

Based on the CHMP review of the available data, the CHMP considers that odronextamab is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.