ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Ordspono 2 mg concentrate for solution for infusion

Ordspono 80 mg concentrate for solution for infusion

Ordspono 320 mg concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Ordspono 2 mg concentrate for solution for infusion

Each single-dose vial contains 2 mg of odronextamab in 1 mL at a concentration of 2 mg/mL.

Ordspono 80 mg concentrate for solution for infusion

Each single-dose vial contains 80 mg of odronextamab in 4 mL at a concentration of 20 mg/mL.

Ordspono 320 mg concentrate for solution for infusion

Each single-dose vial contains 320 mg of odronextamab in 16 mL at a concentration of 20 mg/mL.

Odronextamab is a recombinant human immunoglobulin (Ig)G4-based bispecific antibody that binds to CD20 and CD3. Odronextamab is produced by recombinant DNA technology in Chinese hamster ovary (CHO) cell suspension culture.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate).

Clear to slightly opalescent, colourless to pale yellow solution with a pH of 5.8 and osmolality range of 276-414 mmol/kg for 2 mg/mL (2 mg), and a range of 291-437 mmol/kg for 20 mg/mL (80 mg and 320 mg)

4. CLINICAL PARTICULARS

4.1 Therapeutic 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.

4.2 Posology and method of administration

Ordspono must only be administered under the supervision of a healthcare professional experienced in the diagnosis and treatment of cancer patients and who has access to appropriate medical support to manage severe reactions associated with cytokine release syndrome (CRS) (see section 4.4). At least 1 dose of tocilizumab for use in the event of CRS should be available prior to Ordspono administration for Cycle 1. Access to an additional dose of tocilizumab within 8 hours of use of the previous tocilizumab dose should be available.

Posology

Prophylaxis, premedications, and post-medications for the treatment of patients with r/r FL or r/r DLBCL

Ordspono should be administered to well-hydrated patients.

Premedications must be administered for each dose in Cycle 1 and Cycle 2, Days 1 and 8 and post-medications for Cycle 1, Days 3, 10, and 17 and Cycle 2, Day 2 as described in Table 1 to reduce the risk of cytokine release syndrome (CRS) or infusion-related reactions (IRR) (see section 4.4). Premedications may be continued beyond Cycle 2, Day 8 until the dose is tolerated without experiencing CRS or IRR. In addition, prophylaxis is recommended to reduce the risk of infection (see section 4.4), tumour lysis syndrome (TLS), and corticosteroid-induced gastrointestinal (GI) adverse reactions.

Table 1: Premedications and post-medications for patients with r/r FL or r/r DLBCL

Treatment cycle and day	Medication	Dose	Administration relative to Ordspono infusion
Cycle 1: Days 1, 2, 8, 9, 15, and 16	Corticosteroid	Dexamethasone 10 mg oral or equivalent Omit on days 2, 9, and 16 if infusions are given on consecutive days.	12 to 24 hours prior to infusion
	Corticosteroid	Dexamethasone 20 mg intravenous	1 to 3 hours prior to infusion
	Antihistamine	Diphenhydramine hydrochloride 25 mg oral or intravenous or equivalent antihistamine	30 to 60 minutes prior to infusion
	Antipyretic	Paracetamol 650 mg to 1 000 mg oral	30 to 60 minutes prior to infusion
Cycle 1: Days 3, 10, and 17	Corticosteroid	Dexamethasone 10 mg oral or equivalent	24 hours after infusion
Cycle 2: Day 1	Corticosteroid	Dexamethasone 10 mg oral or equivalent	12 to 24 hours prior to infusion
	Corticosteroid	Dexamethasone 20 mg intravenous	1 to 3 hours prior to infusion
	Antihistamine	Diphenhydramine hydrochloride 25 mg oral or intravenous or equivalent antihistamine	30 to 60 minutes prior to infusion
	Antipyretic	Paracetamol 650 mg to 1 000 mg oral	30 to 60 minutes prior to infusion

Cycle 2: Day 2	Corticosteroid	Dexamethasone 10 mg oral or equivalent	24 hours after infusion
Cycle 2: Day 8	Corticosteroid	Dexamethasone 10 mg* intravenous	1 to 3 hours prior to infusion
	Antihistamine	Diphenhydramine hydrochloride 25 mg oral or intravenous or equivalent antihistamine	30 to 60 minutes prior to infusion
	Antipyretic	Paracetamol 650 mg to 1 000 mg oral	30 to 60 minutes prior to infusion
*If CRS or IRR occurs with the Cycle 2 Day 1 dose, administer dexamethasone 20 mg intravenously for the next dose until the dose is tolerated without experiencing CRS or IRR.			

Recommended dose

The recommended dose for Ordspono is presented in Table 2. For Cycles 1 to 4, a treatment cycle is 21 days. Each dose should only be administered if the previous dose is tolerated. For doses that are not tolerated, refer to Tables 4, 5, and 6.

Ordspono should be administered until disease progression or unacceptable toxicity.

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	r/r DLBCL	
Day of treatment	**Dose of Ordspono**		**Duration of infusion**
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.			

Recommendations for restarting therapy with Ordspono after a dose delay in patients with r/r FL or r/r DLBCL

Table 3 provides recommendations for restarting therapy after a dose delay. For recommendations on restarting therapy after dose delays due to CRS, see Table 4, or due to IRR or TLS, see Table 6.

Table 3: Recommendations for restarting therapy with Ordspono after a dose delay

Cycle	Day	Last dose administered	Time since the last dose administered	Action for next dose
1	1	0.2 mg	Greater than 3 days	Restart from 0.2 mg (Cycle 1, Day 1)
	2	0.5 mg	Less than 2 weeks	Administer next scheduled dose[a]
			2 weeks or longer	Restart from 0.2 mg (Cycle 1, Day 1)
	8 and 9	2 mg	Less than 3 weeks	Administer next scheduled dose[a]
			3 to 4 weeks	Administer 2 mg (Cycle 1, Day 9), then resume the planned treatment schedule.
			Greater than 4 weeks	Restart from 0.2 mg (Cycle 1, Day 1)
	15 and 16	10 mg	Less than 3 weeks	Administer next scheduled dose[a]
			3 to 5 weeks	Administer 10 mg (Cycle 1, Day 16), and then resume the planned treatment schedule.
			Greater than 5 weeks	Restart from 0.2 mg (Cycle 1, Day 1)
2 to 4	1, 8, 15	• r/r FL: 80 mg • r/r DLBCL: 160 mg	Less than 7 weeks	Administer next scheduled dose[a]
			7 to 10 weeks	Administer 10 mg (Cycle 1, Day 16), then resume the planned treatment schedule.
			Greater than 10 weeks	Restart from 0.2 mg (Cycle 1, Day 1)
Maintenance	Every 2 weeks OR Every 4 weeks after CR maintained for 9 months	• r/r FL: 160 mg • r/r DLBCL: 320 mg	Less than 7 weeks	Administer next scheduled dose[a]
			7 to 10 weeks	Administer 10 mg (Cycle 1, Day 16), then resume the planned treatment schedule.
			Greater than 10 weeks	Restart from 0.2 mg (Cycle 1, Day 1)
NOTE: Administer premedications and post-medications as per Table 1.				

Cycle	Day	Last dose administered	Time since the last dose administered	Action for next dose
r/r FL=relapsed or refractory follicular lymphoma; r/r DLBCL=relapsed or refractory diffuse large B-cell lymphoma [a] As per Table 2, resume the treatment schedule without skipping doses.				

Management of adverse reactions in the treatment of patients with r/r FL or r/r DLBCL

Cytokine release syndrome

CRS should be identified based on clinical presentation (see section 4.4). Other causes of fever, hypoxia, and hypotension should be evaluated and treated. If CRS is suspected, withhold Ordspono until CRS resolves. CRS should be managed according to the recommendations in Table 4. Supportive therapy for CRS should be administered, which may include intensive care for severe or life-threatening CRS.

If Grade 1, 2, or 3 CRS occurs, premedications should be administered prior to next dose of Ordspono, and patients should be monitored more frequently. Refer to Table 1 for additional information on premedications.

Table 4: Recommendations for management of cytokine release syndrome

Grade[a]	Presenting symptoms	Actions
Grade 1	Fever ≥ 38 ºC	• Withhold Ordspono infusion. • Manage per current practice guidelines. In cases of advanced age, co-morbidities, fever refractory to antipyretics, consider dexamethasone[b] and/or tocilizumab[c]. • Resume when clinical symptoms of CRS resolve.[d]
Grade 2	Fever ≥ 38 ºC with: Hypotension not requiring vasopressors and/or hypoxia requiring low-flow oxygen[e] by nasal cannula or blow-by	• Withhold Ordspono infusion and administer dexamethasone[b] and/or tocilizumab[c]. • Resume when clinical symptoms of CRS resolve.[d] • For the next dose of Ordspono, monitor more frequently and consider hospitalisation. • For recurrent Grade 2 CRS, manage per Grade 3 CRS.
Grade 3	Fever ≥ 38 ºC with: Hypotension requiring a vasopressor (with or without vasopressin) and/or hypoxia requiring high-flow oxygen[e] by nasal cannula, face mask, non-rebreather mask, or Venturi mask.	• Withhold Ordspono infusion, administer dexamethasone[f] and/or tocilizumab[c], and provide supportive therapy, which may include intensive care. • When clinical symptoms of CRS resolve, the next dose of Ordspono should be at least 5 days following the previous dose as follows: • Hospitalise for the next dose of Ordspono.

Grade[a]	Presenting symptoms	Actions
		• For CRS occurring at Cycle 1, Day 1 or Cycle 1, Day 2, the doses of 0.2 mg or 0.5 mg of Ordspono should be repeated, respectively. • For CRS occurring at Cycle 1, Day 8 or later, reduce to 50% of the last dose received. • If no recurrence, complete step-up dosing (if applicable) and continue administration per Table 2. • If CRS recurs, manage per guidance in this table. If CRS is refractory to dexamethasone and tocilizumab: • Consider alternative anti-cytokine therapy and/or alternative immunosuppressant therapy.
Grade 4	Fever ≥ 38 °C with: Hypotension requiring multiple vasopressors (excluding vasopressin) and/or hypoxia requiring oxygen by positive pressure (e.g., CPAP, BiPAP, intubation, and mechanical ventilation).	• Permanently discontinue Ordspono. • Manage CRS by administering dexamethasone[f] and/or tocilizumab[c] and provide supportive therapy, which may include intensive care. If CRS is refractory to dexamethasone and tocilizumab: • Consider alternative anti-cytokine therapy and/or alternative immunosuppressant therapy.

[a] Based on the American Society for Transplantation and Cellular Therapy (ASTCT) consensus grading for CRS (Lee et al., 2019).
[b] Dexamethasone should be administered at 10-20 mg per day intravenously (or equivalent).
[c] Tocilizumab 8 mg/kg intravenously over 1 hour (not to exceed 800 mg per dose) as needed for CRS management.
[d] If there is a dose delay refer to Table 3 for information on restarting Ordspono after dose delays.
[e] Low-flow oxygen defined as oxygen delivered at < 6 L/minute: high-flow oxygen defined as oxygen delivered at ≥ 6 L/minute.
[f] Dexamethasone should be administered at 10-20 mg intravenously every 6 hours.

Neurologic toxicity

At the first sign of neurologic toxicity, including ICANS, consider neurology evaluation and rule out other causes of neurologic symptoms. Provide supportive therapy, which may include intensive care.

Table 5 provides recommendations for management of ICANS. Table 6 includes recommendations for management of neurologic toxicity excluding ICANS, in addition to other adverse reactions.

Table 5: Recommendations for management of ICANS

Grade[a,b]	Presenting symptoms[b]	Actions
Grade 1	ICE score[c] 7-9 or, depressed level of consciousness: awakens spontaneously	Withhold Ordspono until resolution of ICANS.[d] • Supportive care: o Monitor neurologic symptoms. o Consider neurology consultation and imaging, as clinically indicated. o Consider seizure prophylaxis with non-sedating, antiseizure medicines (such as levetiracetam).

		• Consider dexamethasone. If concurrent CRS, also treat with tocilizumab.[e]
Grade 2	ICE score[c] 3-6 or, depressed level of consciousness: awakens to voice	Withhold Ordspono until resolution of ICANS.[d] • Supportive care as per Grade 1. • 1 dose of dexamethasone 10 mg intravenously and reassess. Repeat every 6 to 12 hours as needed until resolution or baseline. If concurrent CRS, also treat with tocilizumab.[e]
Grade 3	ICE score[c] 0-2 or, depressed level of consciousness: awakens only to tactile stimulus, or seizures, either: • any clinical seizure, focal or generalised that resolves rapidly, or • non-convulsive seizures on electroencephalogram (EEG) that resolve with intervention, or raised intracranial pressure (ICP): focal/local oedema on neuroimaging	Discontinue Ordspono permanently. • Supportive care as per Grade 1. • Dexamethasone 10 mg intravenously every 6 hours or methylprednisolone 1 mg/kg intravenously every 12 hours.[f, g] If concurrent CRS, also treat with tocilizumab.[e]
Grade 4	ICE score[c] 0 or, depressed level of consciousness either: • patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse, or • stupor or coma, or seizures, either: • life-threatening prolonged seizure (> 5 minutes), or • repetitive clinical or electrical seizures without return to baseline in between, or motor findings:	Discontinue Ordspono permanently. • Consider ICU care as clinically indicated, consider mechanical ventilation for airway protection. • Supportive care as per Grade 1. • High-dose corticosteroids.[f, g] • If raised intracranial pressure (ICP)/cerebral oedema, follow standard of care measures to control ICP; consider neurosurgery consultation. If concurrent CRS, also treat with tocilizumab.[e]

	• deep focal motor weakness such as hemiparesis or paraparesis, or raised intracranial pressure (ICP)/cerebral oedema, with signs/symptoms such as: • diffuse cerebral oedema on neuroimaging, or • decerebrate or decorticate posturing, or • cranial nerve VI palsy, or • papilloedema, or • Cushing's triad	

[a] Grade ICANS according to ASTCT ICANS Consensus Grading.
[b] ICANS grade is determined by the most severe event (ICE score, level of consciousness, seizures, motor findings, raised ICP/cerebral oedema) not attributable to any other cause.
[c] If patient is arousable and able to perform ICE Assessment, assess: Orientation (oriented to year, month, city, hospital = 4 points); Naming (name 3 objects, e.g., point to clock, pen, button = 3 points); Following Commands (e.g., "show me 2 fingers" or "close your eyes and stick out your tongue" = 1 point); Writing (ability to write a standard sentence = 1 point); and Attention (count backwards from 100 by ten = 1 point). If patient is unarousable and unable to perform ICE Assessment (Grade 4 ICANS) = 0 points.
[d] If there is a dose delay, refer to Table 3 for information on restarting Ordspono after dose delays.
[e] Tocilizumab 8 mg/kg intravenously over 1 hour (not to exceed 800 mg/dose).
[f] Antifungal prophylaxis is recommended in patients receiving corticosteroids for the treatment of CRS and/or neurologic toxicity, as clinically indicated.
[g] For example, methylprednisolone 1000 mg/day intravenously for 3 days, followed by rapid taper.

Other adverse reactions

Table 6: Dose modifications for other adverse reactions

Adverse reaction	**Severity**	**Ordspono dose modifications**
Infusion-related reactions	Grade 2	Interrupt and manage appropriately. Resume at a 50% rate of infusion and increase as tolerated.
	Grade 3	Interrupt and manage according to standard clinical practice. After resolution of the event, wait 24 hours and repeat the dose (reduce by 50% for doses ≥ 2 mg).
	Grade 4	Permanently discontinue.
Infections	Grades 1 to 4	Withhold Ordspono in patients with active infection until the infection resolves.[a] For Grade 4, consider permanent discontinuation of Ordspono.[a]
Neurologic toxicity excluding ICANS	Grade 2[b] and 3	Withhold Ordspono until neurologic toxicity symptoms improve to Grade 1 or baseline. Provide supportive therapy and consider neurologic evaluation.
	Grade 4	Permanently discontinue Ordspono.
Tumour lysis syndrome	Grade 3 and 4	Withhold Ordspono and manage according to standard clinical practice. After complete resolution:

Adverse reaction	Severity	Ordspono dose modifications
		• For doses ≤ 0.5 mg, restart from 0.2 mg (Cycle 1, Day 1). If no recurrence, continue with the dosing schedule per Table 2. • For doses ≥ 2 mg, resume at 50% of the last dose received. If no recurrence, continue with the dosing schedule per Table 2 without skipping doses. • If TLS recurs, manage per guidance in this table. Maintain at least 2 days between consecutive doses until the end of Cycle 1.
Neutropenia	Absolute neutrophil count less than 0.5×10^9/L	Withhold Ordspono until absolute neutrophil count is 0.5×10^9/L or higher.[a]
Thrombocytopenia	Platelet count less than 50×10^9/L	Withhold Ordspono until platelet count is 50×10^9/L or higher.[a]
Other adverse reactions	Other Grade 3 adverse reaction	Withhold Ordspono until complete resolution, resolution to Grade 1 or baseline then continue dosing.[a]
	Other Grade 4 adverse reaction	Permanently discontinue. Patients with transient Grade 4 laboratory abnormalities may resume treatment[a] upon resolution to Grade 1 or baseline.
Adverse reactions were graded based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 4.03 in Study 1333 and Version 5.0 in Study 1625. [a] If there is a dose delay, refer to Table 3 for recommendations on restarting Ordspono after dose delays. [b] The type of neurologic toxicity should be considered before deciding to withhold Ordspono.		

Special populations

Elderly
No dose adjustment is recommended for elderly patients (see section 5.2).

Renal impairment
No dose adjustment is recommended for patients with renal impairment (see section 5.2).

Hepatic impairment
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). No dose recommendations can be made for patients with severe hepatic impairment (see section 5.2).

Paediatric population
The safety and efficacy of Ordspono in children below 18 years of age have not been established. No data are available.

Method of administration

Ordspono is for intravenous use after dilution only.

- The first cycle of Ordspono is administered as a 4-hour infusion. If Ordspono is tolerated on Cycle 2, Day 1, infusion time can be reduced to 1 hour for all subsequent doses. Refer to Table 2.

- Ordspono should be administered as an intravenous infusion through a dedicated infusion line.
- Ordspono must not be administered as intravenous push or bolus.
- See Table 1 for premedications and post-medications.
- For doses that are not tolerated, refer to Tables 4, 5, and 6 for management guidance.

Ordspono must be diluted using aseptic technique.

For instructions on dilution of Ordspono before administration, see section 6.6. Compatible materials for tubing are also described in section 6.6. It is recommended to use a 0.2-micron or 5-micron polyethersulfone (PES) filter.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded. If an Albumin (Human) solution is used in cases as suggested under section 6.6, the name and batch number should be clearly recorded to ensure full traceability.

Cytokine release syndrome (CRS) and infusion-related reactions (IRR)

Ordspono can cause cytokine release syndrome (CRS), which may be serious or life-threatening (see section 4.8).

Clinical signs and symptoms of CRS included, but were not limited to, fever, hypotension, hypoxia, tachycardia, chills, dyspnoea, and headache. CRS events occurred predominantly in Cycle 1. Transient elevation of liver enzymes has been observed in patients experiencing CRS. See sections 4.2 and 4.8 for CRS monitoring and management guidance.

Therapy according to the step-up dosing schedule should be initiated, premedications should be administered to reduce the risk of CRS, and patients should be monitored accordingly for potential CRS following Ordspono. The step-up dosing schedule and premedications were established to mitigate the risk of CRS and should be followed (see section 4.2).

Monitoring and management of CRS
Patients should be monitored for signs and symptoms of CRS during and following Ordspono administration for immediate management and should 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. At the first sign of CRS, patients should be immediately evaluated for hospitalisation, managed per the guidance provided in Table 4, and supportive care should be administered; withhold or permanently discontinue Ordspono based on severity. Patients should be counselled to seek immediate medical attention should signs or symptoms of CRS occur at any time.

Patients who experience CRS (or other adverse reactions that impair consciousness) should be evaluated and advised not to drive and to refrain from operating heavy or potentially dangerous machinery until resolution (see section 4.7).

Some manifestations of infusion-related reactions (IRR) may be clinically indistinguishable from manifestations of CRS. For IRR, withhold, slow the rate of infusion, or permanently discontinue Ordspono based on severity of reaction (see section 4.2).

Serious infections

Ordspono can cause serious or fatal infections (see section 4.8).

Monitoring and management of serious infections
Patients should be monitored before and during treatment with Ordspono treatment for the emergence of possible bacterial, fungal, and new or reactivated viral infections and treated appropriately. Ordspono should not be administered in the presence of active infection. Caution should be exercised when considering the use of Ordspono in patients with a history of recurring or chronic infections. Administer prophylactic antimicrobials as appropriate.

Prophylactic treatment for *Pneumocystis jirovecii* pneumonia (PJP) is recommended for all patients. Prophylactic treatment is recommended for patients with a history of herpes virus infections and cytomegalovirus (CMV) infections. Antiviral treatment is recommended for patients with positive hepatitis B surface antigen, hepatitis B core antibody, and/or measurable viral load. Intravenous immunoglobulin (IVIG) should be considered per guidelines.

Febrile neutropenia has been reported during treatment with Ordspono. In the event of febrile neutropenia, patients should be evaluated for infection and managed with antibiotics, fluids, and other supportive care, according to local guidelines.

Withhold Ordspono or consider permanent discontinuation of Ordspono based on severity (see section 4.2).

Neurologic toxicity

Neurologic toxicities, such as immune effector cell-associated neurotoxicity syndrome (ICANS), aphasia, and encephalopathy, which may be severe, occurred following treatment with Ordspono.

Monitoring and management of neurologic toxicities
Patients should be monitored for signs and symptoms of neurologic toxicity, evaluated, and provided supportive care; withhold or permanently discontinue Ordspono based on severity (see section 4.2*).*

Patients should be counselled to seek medical attention should signs or symptoms of neurologic toxicity occur.

Tumour lysis syndrome (TLS)

TLS has been reported in patients receiving odronextamab (see section 4.8). Patients with high tumour burden, rapidly proliferative tumours, or renal dysfunction are at greater risk of tumour lysis syndrome. Patients at an increased risk for TLS should have adequate hydration and prophylactic anti-hyperuricemics (e.g., allopurinol or rasburicase) prior to the administration of odronextamab.

Monitoring and management of TLS
Patients should be monitored for signs and symptoms of TLS, including blood chemistries, and any abnormalities should be managed promptly.

Pneumonitis/Interstial lung disease (ILD)

Pneumonitis/ILD, which may be life-threatening or fatal, has been reported in patients receiving odronextamab and should be considered in case of respiratory symptoms without any causative pathogen.

Patient card

The Patient Card describes the common signs and symptoms of CRS and neurologic toxicity, including ICANS, and provides instructions on when a patient should seek immediate medical

attention. The prescriber must discuss the risks of Ordspono therapy with the patient. Patients should be provided with the Patient Card, instructed to carry it at all times, and show it to all of their healthcare providers.

Immunisation

Live and/or live-attenuated vaccines should not be given concurrently with Ordspono. Studies have not been conducted in patients who recently received live vaccines.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed. Initiation of treatment with Ordspono causes a transient elevation of cytokines, which 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 (e.g., warfarin, cyclosporine, or theophylline). On initiation of therapy with Ordspono in patients being treated with CYP450 substrates with a narrow therapeutic index, therapeutic monitoring should be considered.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception

Females of reproductive potential should use effective contraception during treatment with Ordspono and for at least 6 months after the last dose.

Pregnancy

There are no available data on the use of Ordspono in pregnant women. No animal reproductive or developmental toxicity studies have been conducted with odronextamab. Human immunoglobulin G (IgG) is known to cross the placenta; therefore, odronextamab has the potential to be transferred from the mother to the developing foetus. Based on its mechanism of action, odronextamab may cause foetal harm, including B-cell lymphocytopenia, when administered to a pregnant woman (see section 5.1). Ordspono is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breast-feeding

There is no information regarding the presence of odronextamab in human milk, the effects on the breastfed infant, or the effects on milk production. It is known that human IgG can be secreted in human milk. Women should be advised not to breastfeed during treatment with Ordspono and for at least 6 months after the last dose due to the potential risk for serious adverse reactions in the breastfed child.

Fertility

No human data on the effect of odronextamab on fertility are available. Animal studies do not indicate harmful effects on male or female reproductive organs or fertility parameters (see section 5.3).

4.7 Effects on ability to drive and use machines

Ordspono has minor influence on the ability to drive and use machines. Patients who experience CRS (or other adverse reactions that impair consciousness) should be evaluated and advised not to drive and to refrain from operating heavy or potentially dangerous machinery until resolution.

4.8 Undesirable effects

Summary of safety profile

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%).

The most common serious adverse reactions were cytokine release syndrome (14%), pneumonia (9%), COVID-19 (9%), and pyrexia (6%).

The frequency of infusion interruption of Ordspono due to an adverse reaction was 16%.
The frequency of treatment discontinuation due to an adverse reaction was 14%. The most common adverse reactions leading to discontinuation were COVID-19 (2.4%), pneumonia (1.3%), and encephalopathy (0.8%).

Tabulated list of adverse reactions

Unless otherwise stated, the frequencies of adverse reactions are based on all-cause adverse event frequencies identified in a pooled safety population of 372 patients who received odronextamab as a single agent in two open-label, multi-centre studies (Study 1333 and Study 1625), including 153 patients with r/r FL and 219 patients with r/r DLBCL. The median exposure to odronextamab was 20.4 weeks (range: 0.4 to 195.7 weeks) (see section 5.1).

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.

The adverse reactions are listed below in Table 7 by MedDRA system organ class (SOC) and categories of frequency. Frequency categories are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100), rare (≥ 1/10 000 to < 1/1 000), very rare (< 1/10 000) and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in decreasing order of frequency by SOC and preferred term.

Table 7: Adverse reactions in patients treated with Ordspono

System organ class **preferred term**	**All Grades**	**Grades 3 or 4**
Infection and infestations		
COVID-19 infection[a]	Very common	Common
Pneumonia[b]	Very common	Very common
Cytomegalovirus infection[c]	Very common	Common
Upper respiratory tract infection[d]	Very common	Uncommon
Urinary tract infection	Very common	Common
Herpes virus infection[e]	Very common	Common
Respiratory tract infection[f]	Common	Common
Fungal infection[g]	Common	Uncommon
Sinusitis	Common	Uncommon
Sepsis[h]	Common	Common

System organ class preferred term	All Grades	Grades 3 or 4
Bacteraemia	Common	Common
Blood and lymphatic system disorders		
Anaemia	Very common	Very common
Neutropenia	Very common	Very common
Thrombocytopenia	Very common	Very common
Leukopenia	Very common	Common
Lymphopenia	Very common	Very common
Febrile neutropenia	Common	Common
Immune system disorders		
Cytokine release syndrome[i]	Very common	Common
Metabolism and nutrition disorders		
Hypokalaemia	Very common	Common
Decreased appetite	Very common	Uncommon
Hyperglycaemia	Very common	Common
Hyponatraemia	Very common	Common
Hypophosphataemia	Very common	Common
Hypomagnesaemia	Common	Not reported
Hypoalbuminaemia	Common	Uncommon
Tumour lysis syndrome	Uncommon	Uncommon
Psychiatric disorders		
Insomnia	Very common	Uncommon
Mental status changes[j]	Common	Common
Nervous system disorders		
Headache	Very common	Uncommon
Neuropathy peripheral	Common	Uncommon
Aphasia[k]	Uncommon	Uncommon
Neurotoxicity	Uncommon	Uncommon
Immune effector cell-associated neurotoxicity syndrome[l]	Uncommon	Not reported
Cardiac disorders		
Tachycardia	Common	Common
Vascular disorders		
Hypotension	Very common	Common
Respiratory, thoracic and mediastinal disorders		
Cough	Very common	Not reported
Dyspnoea	Very common	Uncommon

System organ class preferred term	All Grades	Grades 3 or 4
Interstitial lung disease	Common	Common
Gastrointestinal disorders		
Diarrhoea	Very common	Common
Nausea	Very common	Uncommon
Abdominal pain[m]	Very common	Common
Constipation	Very common	Not reported
Vomiting	Very common	Uncommon
Skin and subcutaneous tissue disorders		
Rash[n]	Very common	Common
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain	Very common	Common
General disorders and administration site conditions		
Pyrexia	Very common	Common
Fatigue[o]	Very common	Common
Oedema[p]	Very common	Common
Investigations		
Alanine aminotransferase increased	Very common	Common
Aspartate aminotransferase increased	Very common	Common
Gamma-glutamyltransferase increased	Common	Common
Blood bilirubin increased	Common	Common
Injury, poisoning and procedural complications		
Infusion-related reaction[i]	Very common	Common

Adverse reactions were graded based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 4.03 in study 1333 and Version 5.0 in study 1625. CRS was graded using American Society for Transplantation and Cellular Therapy (ASTCT) consensus criteria (Lee et al., 2019).)

[a] Includes COVID-19 and COVID-19 pneumonia.

[b] Includes bacterial, fungal, and viral pneumonia, including CMV and PJP.

[c] Includes CMV infections, reactivations, and viraemia.

[d] Includes nasopharyngitis, upper respiratory tract infection, and viral upper respiratory tract infection.

[e] Includes herpes virus infection and herpes zoster.

[f] Includes bacterial and viral infections.

[g] Includes systemic, mucosal, and skin fungal infections.

[h] Includes bacterial sepsis, pseudomonal sepsis, sepsis, and septic shock.

[i] CRS and IRR events were reported per investigator's discretion with guidance based on time of occurrence from the start of the infusion. Data for these events are reported in patients treated with the recommended step-up dosing regimen (N=197).

[j] Includes mental status changes, cognitive disorder, encephalopathy, somnolence, confusional state, disturbance in attention, and disorientation.

[k] Includes aphasia and dysarthria.

System organ class preferred term	All Grades	Grades 3 or 4
[l] Immune Effector Cell-Associated Encephalopathy (ICE) scoring was not systematically performed. [m] Includes abdominal distension, abdominal discomfort, abdominal pain, abdominal pain lower, and abdominal pain upper. [n] Includes dermatitis, erythema, rash maculo-papular, rash pruritic, and toxic skin eruption. [o] Includes asthenia, fatigue, malaise, and lethargy. [p] Includes localised oedema, generalised oedema, and pulmonary oedema.		

Description of selected adverse reactions

Cytokine release syndrome (CRS)

In patients with r/r FL treated with the recommended step-up dosing regimen, the rate of CRS was 58%, including Grade 1 CRS (47%), Grade 2 CRS (10%), and Grade 3 CRS (1.3%). Recurrent CRS occurred in 32% of patients with r/r FL. In patients with r/r DLBCL treated with the recommended step-up dosing regimen, the rate of CRS was 52%, including Grade 1 CRS (35%), Grade 2 CRS (16%), and Grade 3 CRS (0.8%). Recurrent CRS occurred in 20% of patients with r/r DLBCL.

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.

Of patients who experienced CRS, 96% had an initial CRS event during the step-up dosing or with the first 80-mg dose for r/r FL or 160-mg dose for r/r DLBCL; 3.7% had their first CRS event after their second 80-mg dose for r/r FL or 160-mg dose for r/r DLBCL.

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). The median time to onset of CRS from the end of infusion in Cycle 1, Day 1 or Day 2 was 6 hours (range: -2.4 hours to 4 days), Cycle 1, Day 8 or Day 9 was 22 hours (range: 3.7 hours to 5 days), and Cycle 1, Day 15 or Day 16 was 22 hours (range: -3.4 hours to 9 days). Transient elevated liver enzymes (ALT or AST > 3 x ULN) were concurrent with CRS in 6.5% of patients with CRS. One patient (0.5%) discontinued due to CRS.

99% of CRS events resolved, and the median duration of CRS was 2 days (range: 1 to 10 days).

24% of patients treated with the recommended step-up dosing regimen received tocilizumab, 26% received corticosteroids, and 13% received both tocilizumab and corticosteroids to treat CRS.

Hospitalisations due to CRS in patients treated with the recommended step-up dosing regimen occurred in 14% of patients, and the median duration was 2.0 days (range 1.0 to 9.0 days).

Serious infections

Among 153 patients with r/r FL who received Ordspono, serious infections occurred in 44%, with Grade 3 infections in 27% and Grade 4 infections in 2.6% of patients. Infections that were fatal within 90 days of the last dose occurred in 8% (13/153) of patients, and of these infections, 62% (8/13) were due to COVID-19 infection. The most common Grade 3 or greater serious infections were COVID-19 (9%), pneumonia (8%), COVID-19 pneumonia (7%), cytomegalovirus infection (3.3%), urinary tract infection (2.6%), sepsis (2.6%) and cytomegalovirus infection reactivation (2.0%).

Among 219 patients with r/r DLBCL who received Ordspono, serious infections occurred in 33%, with Grade 3 infections in 20% and Grade 4 infections in 0.9% of patients. Infections that were fatal within 90 days of the last dose occurred in 9% (19/219) of patients, and of these infections, 42% (8/19) were due to COVID-19 infection. The most common Grade 3 or greater serious infections were pneumonia (10%), COVID-19 (6%), *Pneumocystis jirovecii* pneumonia (3.7%), sepsis (3.2%), and COVID-19 pneumonia (2.7%).

Neurologic toxicity

Among 372 patients with r/r FL or r/r DLBCL who received ORDSPONO, 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. Event of ICANS (Grade 2) was reported in one patient (0.3%).

Tumour lysis syndrome

Among 372 patients with r/r FL or r/r DLBCL who received ORDSPONO, TLS was reported in 0.5% of patients (N=2); both events were Grade 3. For these events, TLS onset was on Day 2 and Day 7, and both resolved within 2 days.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Overdose, at more than twice the recommended dose, has been reported in patients taking Ordspono. Some of these patients experienced symptoms consistent with the known risks of Ordspono (see section 4.8). In case of overdose, patients should be closely monitored for signs or symptoms of adverse reactions, and appropriate symptomatic treatment instituted.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents; other monoclonal antibodies and antibody drug conjugates, ATC code: not yet assigned

Mechanism of action

Odronextamab is a human IgG4-based bispecific antibody that binds to CD20, a B-cell surface antigen present on normal and malignant B cells and CD3, a T-cell antigen associated with the T-cell receptor complex. Simultaneous engagement of both arms of odronextamab results in formation of a synapse between the T cell and the CD20-expressing cell, resulting in T-cell activation and generation of polyclonal cytotoxic T-cell response, which result in redirected lysis of the targeted cells, including malignant B cells.

Pharmacodynamic effects

Circulating B-cell count

Following administration of the recommended doses of odronextamab, median circulating B cells decreased to undetectable levels (< 1 cells/microliter) by Week 4 (Cycle 2, Day 1, after the first 80-mg

dose for r/r FL or 160-mg dose for r/r DLBCL) administered in patients who had detectable B cells at baseline. The B-cell depletion was sustained while patients remained on treatment.

Cytokine concentration

Concentrations of cytokines (IL-2, IL-6, IL-10, TNF-α, and IFN-γ) in serum were measured. Transient elevation of circulating cytokines was observed at dose levels of 0.2 mg and above. After administration of the recommended step-up dosing regimen of odronextamab, the highest elevation of systemic cytokine concentrations was observed within 24 hours after each intravenous infusion in Cycle 1, typically observed in the first two weeks. The elevated cytokine concentrations generally returned to baseline prior to the next infusion during the step-up dosing period (Cycle 1). Limited cytokine release was observed following subsequent doses.

Immunogenicity

During treatment in Study 1625 and Study 1333, anti-odronextamab antibodies (ADA) were detected in 1.5% (6/400) of patients. No neutralizing antibodies were observed. No evidence of ADA impact on pharmacokinetics or safety was observed, however, data are still limited.

Clinical efficacy and safety

Relapsed or refractory follicular lymphoma (r/r FL)

The efficacy of Ordspono was evaluated in 128 patients with r/r FL (based on WHO Classification 2017) in an open-label, multi-centre, non-randomized, multi-cohort study: Study 1625. The trial included adult patients with histologically confirmed grade 1-3a follicular lymphoma whose disease relapsed or became refractory after at least 2 prior lines of systemic therapy, including an anti-CD20 antibody and an alkylating agent. This study included patients with adequate bone marrow and organ function. The study excluded patients with central nervous system (CNS) involvement or prior allogeneic stem cell transplantation.

Following step-up dosing in Cycle 1, patients were treated with Ordspono 80 mg weekly until the end of Cycle 4 followed by 160 mg every 2 weeks until disease progression or unacceptable toxicity. Patients who maintained complete response (CR) for 9 months switched from maintenance dosing of 160 mg every 2 weeks to 160 mg every 4 weeks.

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

Efficacy was established based on the primary efficacy endpoint of objective response rate (ORR) and the secondary endpoint of duration of response (DOR) as assessed by an independent central review committee (IRC) using 2014 Lugano criteria (see Table 8).

Table 8: Efficacy results in patients with r/r FL in Study 1625

Efficacy endpoints	**Ordspono (N=128)**
Objective response rate (ORR), % (n) (95% CI)	80% (103) (73, 87)

Efficacy endpoints	Ordspono (N=128)
Complete response (CR) rate, % (n) (95% CI)	73% (94) (65, 81)
Partial response (PR) rate, % (n) (95% CI)	7% (9) (3.3, 13)
Duration of response (DOR)[a]	N=103
Patients with event, % (n)	42% (43)
Median, months (95% CI)	23 (18, NE)
Duration of complete response (DOCR)[b]	N=94
Patients with event, % (n)	38% (36)
Median, months (95% CI)	25 (20, NE)

CI=confidence interval; K-M=Kaplan-Meier; NE=Not estimable.

[a] DOR is defined as the time from the initial occurrence of a documented PR or CR until the patient experiences an event (documented disease progression or death due to any cause, whichever occurs first).

[b] DOCR is defined as the time from the initial occurrence of a documented CR until the patient experiences an event (documented disease progression or death due to any cause, whichever occurs first).

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

The median follow-up for DOR was 17.6 months (95% CI: 14.8, 29 months).

Relapsed or refractory diffuse large B-cell lymphoma (r/r DLBCL)

The efficacy of Ordspono was evaluated in 187 patients with r/r DLBCL (based on WHO Classification 2017) in two open-label, multi-centre, non-randomized, multi-cohort studies: Study 1625 (n=127) and Study 1333 (n=60). Both trials included adult patients with r/r DLBCL after at least 2 prior lines of systemic therapy, including an anti-CD20 antibody and an alkylating agent. Study 1333 included patients who progressed after CAR-T therapy. Both studies included patients with adequate bone marrow and organ function. Both studies excluded patients with central nervous system (CNS) involvement or prior allogeneic stem cell transplantation.

Following step-up dosing in Cycle 1, patients were treated with Ordspono 160 mg weekly until the end of Cycle 4 followed by 320 mg every 2 weeks until disease progression or unacceptable toxicity. Patients who maintained CR for 9 months switched from 320 mg every 2 weeks to 320 mg every 4 weeks.

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

Among the 127 patients with r/r DLBCL in Study 1625, the median age was 67 years (range: 24 to 88), 57% were age 65 or older, 60% were male, 48% were White, 42% were Asian, 32% with ECOG PS 0, and 68% with ECOG PS 1. The median number of prior therapies was 2 (range: 2 to 8). The diagnosis was de novo DLBCL in 76%, DLBCL transformed from indolent lymphoma in 19%, and Richter's transformation in 6%. Of these patients, 87% had disease refractory to last line of therapy, 55% had primary refractory disease, 91% had DLBCL NOS, 9% had high-grade B-cell lymphoma with double-hit or triple-hit gene rearrangements (MYC with BCL2 and/or BCL6 rearrangements), 56% had an International Prognostic Index (IPI) of 3 (high-intermediate) to 5 (high), 44% had activated B-cell-like (ABC) DLBCL/non-germinal centre B-cell-like (non-GCB) DLBCL, 78% were refractory to an anti-CD20 antibody in an earlier line of therapy, 65% were double refractory (to anti-CD20 antibody and alkylating agents) in any line of therapy, and 17% had prior HSCT.

Efficacy was established on the basis of the primary efficacy endpoint of objective response rate (ORR) and secondary endpoint of duration of response (DOR) as assessed by an independent central review committee (IRC) using 2014 Lugano criteria (see Table 9).

Table 9: Efficacy results in patients with r/r DLBCL in Study 1625

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

CI=confidence interval; K-M=Kaplan-Meier; NE=Not estimable.

[a] DOR is defined as the time from the initial occurrence of a documented PR or CR until the patient experiences an event (documented disease progression or death due to any cause, whichever occurs first).

[b] DOCR is defined as the time from the initial occurrence of a documented CR until the patient experiences an event (documented disease progression or death due to any cause, whichever occurs first).

The first response assessment occurred at 12 weeks. The median time to first response was 2.6 months (range: 0.8 to 6.4 months) and the median time to first complete response was 2.6 months (range: 1.4 to 8.1 months).

The median follow-up for DOR was 30 months (95% CI :14.7, 32.2 months).

Study 1333: r/r DLBCL after CAR-T therapy

In Study 1333, of the 60 r/r DLBCL patients who relapsed or were refractory to CAR-T therapy, the median age was 63 years (range: 27 to 82), 45% were age 65 or older, 65% were male, 77% were White, 3.3% were Black, 8% were Asian, 23% with ECOG PS 0, and 77% with ECOG PS 1. The median number of systemic prior therapies was 3 (range: 2 to 9), and 72% were refractory to CAR-T for any line of therapy.

Efficacy was established based on the primary efficacy endpoint of objective response rate (ORR) and the secondary endpoint of duration of response (DOR) as assessed by an independent central review committee (IRC) using 2014 Lugano criteria (see Table 10).

Table 10: Efficacy results in patients with r/r DLBCL in Study 1333

Efficacy endpoints	Ordspono (N=60)
Objective response rate (ORR), % (n) (95% CI)	48% (29) (35, 62)
Complete response (CR), % (n) (95% CI)	32% (19) (20, 45)

Partial response (PR), % (n) (95% CI)	17% (10) (8, 29)
Duration of response (DOR)[a]	N=29
Patients with event, % (n)	38% (11)
Median, months (95% CI)	15 (3, NE)
CI=confidence interval; K-M=Kaplan-Meier; NE=Not estimable. [a] DOR is defined as the time from the initial occurrence of a documented PR or CR until the patient experiences an event (documented disease progression or death due to any cause, whichever occurs first).	

The median duration of follow-up for DOR was 15 months (95% CI: 4.3, 16.3 months).

Paediatric population

The European Medicines Agency has deferred the obligation to submit results of studies with Ordspono in one or more subsets of the paediatric population in the Treatment of mature B cell malignancies (see section 4.2 for information on paediatric use).

Conditional approval

This medicinal product has been authorised under a so-called 'conditional approval' scheme. This means that further evidence on this medicinal product is awaited. The European Medicines Agency will review new information on this medicinal product at least every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

Pharmacokinetics (PK) of odronextamab was characterized in patients with B-cell non-Hodgkin lymphoma (B-NHL) over a dose range from 0.03 mg to 320 mg following intravenous infusion. During the step-up dosing period, the disposition of odronextamab is concentration- and time-dependent. As dose levels increase with continued treatment to ≥ 80 mg, the PK profile of odronextamab becomes linear and dose-proportional at steady-state. The exposure parameters at doses ≥ 80 mg were approximately dose-proportional (see Table 11). PK was similar across the B-NHL patient populations evaluated.

Table 11: Predicted exposure parameters of recommended dose for odronextamab

	C_{max} (mg/L)[a]	**C_{trough} (mg/L)[a]**	**AUCτ (mg*day/L)[a,b]**
Follicular lymphoma			
80 mg weekly (Week 12, Cycle 4, Day 15)	44.7 (18.4, 71.4)	28.8 (8.55, 47.9)	238 (88.1, 389)
160 mg every 2 weeks (steady-state, Weeks 24-26)	67.9 (29.8, 105)	32.6 (6.95, 55.6)	600 (216, 954)
Diffuse large B-cell lymphoma			
160 mg weekly (Week 12, Cycle 4, Day 15)	98.2 (49.2, 151)	66.9 (27.6, 103)	544 (254, 825)
320 mg every 2 weeks (steady-state, Weeks 24-26)	147 (82.2, 223)	77.9 (35.2, 126)	1380 (672, 2090)
[a] Values are median and 5th and 95th percentiles from a simulation of 507 subjects with B-NHL. [b] AUCτ for the specified dosing interval.			

Distribution

The estimated geometric mean (CV%) of volume of distribution at steady-state (Vd_{ss}) of odronextamab is 9.34 L (CV% 48.5).

Biotransformation

Odronextamab is expected to be metabolized into small peptides by catabolic pathways.

Elimination

Odronextamab elimination is mediated by two parallel processes, a linear, non-saturable catabolic process and a nonlinear, saturable target-mediated pathway, with higher clearance at lower doses.

Following administration of the last dose of 160 mg once every 2 weeks at steady-state, the time to reach a lower limit of quantification (LLOQ, 0.00313 mg/L) was 19 weeks, and the time to reach 1% of the median C_{max} of 160 mg once every 2 weeks dose was 12 weeks.

Following administration of the last dose of 320 mg once every 2 weeks at steady-state, the time to reach the LLOQ (0.00313 mg/L) was 24 weeks, and the time to reach 1% of the median C_{max} of 320 mg once every 2 weeks dose was 16 weeks.

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.

Renal impairment

The population pharmacokinetics analysis of odronextamab showed that creatinine clearance (CrCL) does not affect the pharmacokinetics of odronextamab. No clinically relevant differences in exposure to odronextamab were observed in patients with normal renal function and with mild (N=178; CrCL ≥ 60 to < 90 mL/min), moderate (N=110; CrCL ≥ 30 to < 60 mL/min), and severe (N=4; CrCL ≥ 15 to < 30 mL/min) renal impairment.

Hepatic impairment

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.

5.3 Preclinical safety data

No carcinogenicity or genotoxicity studies have been conducted with odronextamab.

No specific studies have been conducted to evaluate potential effects of odronextamab on fertility. No adverse effects on male or female reproductive organs and no effects on semen analysis or menstrual cyclicity were observed in a 16-week repeat-dose toxicology study in cynomolgus monkeys.

No developmental toxicity studies in animals have been conducted with odronextamab. Based on its mechanism of action, odronextamab may cause foetal B-cell lymphocytopenia that may be harmful to the foetus and transient CRS that may be harmful to pregnancy maintenance.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

L-histidine
L-histidine monohydrochloride monohydrate
Sucrose
Polysorbate 80 (E433)
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vial

3 years

Diluted solution

Chemical and physical in-use stability has been demonstrated for the diluted Ordspono infusion solution as follows:

- in a refrigerator (2 °C to 8 °C) for all doses for up to 24 hours.
- at room temperature (20 °C to 25 °C) for up to 6 hours for the 0.2-mg dose with Albumin (Human).
- at room temperature (20 °C to 25 °C) for up to 12 hours for doses of 0.5 mg or greater.

Discard diluted infusion solution if storage time exceeds these limits.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 °C to 8 °C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store in a refrigerator (2 °C to 8 °C).
Do not freeze.
Keep the vial in the outer carton in order to protect from light.
For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

2 mg concentrate for solution for infusion

1 mL of concentrate for solution for infusion in a 2 mL Type I clear glass vial with a grey chlorobutyl stopper with coating and an aluminium seal cap with a dark blue flip-off button containing 2 mg of odronextamab.

Pack of one vial.

80 mg concentrate for solution for infusion

4 mL of concentrate for solution for infusion in a 10 mL Type I clear glass vial with a grey chlorobutyl stopper with coating and an aluminium seal cap with a light green flip-off button containing 80 mg of odronextamab.

Pack of one vial.

320 mg concentrate for solution for infusion

16 mL of concentrate for solution for infusion in a 20 mL Type I clear glass vial with a grey chlorobutyl stopper with coating and an aluminium seal cap with a white flip-off button containing 320 mg of odronextamab.

Pack of one vial.

6.6 Special precautions for disposal and other handling

General precautions

Proper aseptic technique throughout the handling of this medicinal product should be followed. Ordspono contains no preservative and is intended for single-dose only. Discard any unused portion left in the vial. Do not shake.

Instructions for dilution

Visually inspect for particulate matter and discoloration prior to administration. Ordspono is a clear to slightly opalescent, colourless to pale yellow solution. Discard the vial if the solution is cloudy, discoloured, or contains particulate matter.

Preparation of 0.2-mg dose

- Prepare Albumin (Human) in sodium chloride 9 mg/mL (0.9%) solution for injection in a 100-mL intravenous bag [polyvinyl chloride (PVC) or polyolefin (PO)] as per Table 12 below.
  - **Note:** Albumin (Human) is only required for the 0.2-mg dose to prevent adsorption of odronextamab to the intravenous filter. When Albumin (Human) is used, please see Traceability in section 4.4.
- The final Albumin (Human) concentration should be 0.04%.

Table 12: Examples of Albumin (Human) concentration and volumes required for the 0.2-mg dose

Albumin (Human) concentration[a]	Albumin (Human) volume for addition to a 100 mL sodium chloride 9 mg/mL (0.9%) solution for injection, infusion bag
5%	0.8 mL
20%	0.2 mL
25%	0.16 mL
[a] Albumin (Human): use concentration as per local availability. Examples include but are not restricted to the following strengths: 5%, 20%, or 25%.	

- Mix the Albumin (Human) and sodium chloride 9 mg/mL (0.9%) solution for injection by gentle inversion. Do not shake.
- Obtain 1 vial of 2 mg Ordspono.
- Withdraw 0.1 mL from the 2-mg Ordspono vial using a 1-mL syringe and add into the prepared 100-mL intravenous bag.
- Mix diluted solution by gentle inversion. Do not shake.

Preparation of 0.5-mg dose

- Obtain a 50-mL intravenous bag (PVC or PO) containing sodium chloride 9 mg/mL (0.9%) solution for injection.
- Obtain 1 vial of 2 mg Ordspono.

- Withdraw 0.25 mL from the 2-mg Ordspono vial using a 1-mL syringe and add into the 50-mL intravenous bag.
- Mix diluted solution by gentle inversion. Do not shake.

Preparation of 1-mg or above dose

- Obtain a 50- or 100-mL intravenous bag (PVC or PO) containing sodium chloride 9 mg/mL (0.9%) solution for injection.
- Obtain the required number of vials and withdraw the appropriate volume of Ordspono.
  - Refer to Table 13 for the specific volume for the intended dose.
  - Refer to Table 14 for the specific volume for dose modifications (see section 4.2).
- Add the appropriate volume of Ordspono to the intravenous bag.
- Mix diluted solution by gentle inversion. Do not shake.

Summary tables for dilution prior to administration

Table 13: Ordspono volumes for addition to the infusion bag (standard doses)

Ordspono dose (mg)	Amount of Ordspono per vial (mg)	Concentration of vial (mg/mL)	Total volume of Ordspono to prepare dose (mL)	Albumin (Human) required	Sodium chloride 9 mg/mL (0.9%) solution for injection, infusion bag (PO or PVC) volume (mL)
0.2	2	2	0.1	Yes	100
0.5	2	2	0.25	No	50
2	2	2	1	No	50 or 100
10	2	2	5	No	50 or 100
80	80	20	4	No	50 or 100
160	80	20	8	No	50 or 100
320	320	20	16	No	50 or 100

Table 14: Other Ordspono volumes for addition to the infusion bag for dose modifications

Ordspono dose (mg)	Amount of Ordspono per vial (mg)	Concentration of vial (mg/mL)	Total volume of Ordspono (mL)	Albumin (Human) required	Sodium chloride 9 mg/mL (0.9%) solution for injection, infusion bag (PO or PVC) volume (mL)
1	2	2	0.5	No	50 or 100
5	2	2	2.5	No	50 or 100
40	80	20	2	No	50 or 100

For storage conditions of the diluted solution in infusion bags, see section 6.3.

Method of administration

Ordspono is for intravenous use after dilution only. Ordspono must be diluted using aseptic technique.

- The first cycle of Ordspono is administered as a 4-hour infusion. If Ordspono is tolerated on Cycle 2, Day 1, infusion time can be reduced to 1 hour for all subsequent doses.
- Ordspono must not be administered as intravenous push or bolus.
- See Table 1 for premedications and post-medications.
- For doses that are not tolerated, refer to Tables 4, 5, and 6 for management guidance.

After Ordspono has been diluted as instructed above, administer as follows:
- Connect the prepared intravenous infusion bag containing the final Ordspono solution to intravenous tubing constructed of polyvinyl chloride (PVC), polyethylene (PE)-lined PVC, or polyurethane (PU). It is recommended to use a 0.2-micron or 5-micron polyethersulfone (PES) filter.
- Prime with Ordspono to the end of the intravenous tubing.
- Do not mix Ordspono with other medicinal products or concurrently administer other medicinal products through the same intravenous line.
- Upon completion of Ordspono infusion, flush the infusion line with adequate volume of sodium chloride 9 mg/mL (0.9%) solution for injection to ensure that the entire contents of the infusion bag are administered.

Disposal

The release of pharmaceuticals into the environment should be minimised. Medicinal products should not be disposed of via wastewater and disposal through household waste should be avoided.

The following points should be strictly adhered to regarding the use and disposal of syringes and other medicinal sharps:
- Needles and syringes should never be reused.
- Place all used needles and syringes into a sharps container (puncture-proof disposable container).

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Regeneron Ireland Designated Activity Company (DAC)
One Warrington Place
Dublin 2
D02 HH27
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1843/001
EU/1/24/1843/002
EU/1/24/1843/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Regeneron Pharmaceuticals, Inc.
81 Columbia Turnpike
Rensselaer, NY 12144
United States

Name and address of the manufacturer responsible for batch release

Regeneron Ireland DAC
Raheen Business Park
Limerick
Ireland

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in Article 9 of Regulation (EC) No 507/2006 and, accordingly, the marketing authorisation holder (MAH) shall submit PSURs every 6 months.

The requirements for submission of PSURs 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.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. 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

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

This being a conditional marketing authorisation and pursuant to Article 14a(4) 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 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	November 2028
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.	September 2031

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Ordspono 2 mg concentrate for solution for infusion
odronextamab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 2 mg odronextamab in 1 mL at a concentration of 2 mg/mL.

3. LIST OF EXCIPIENTS

Excipients: L-histidine, L-histidine monohydrochloride monohydrate, sucrose, polysorbate 80, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

concentrate for solution for infusion
2 mg/1 mL

1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For single use only
Read the package leaflet before use
For intravenous use after dilution

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not shake the vial

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.

Do not freeze.
Keep the vial in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Regeneron Ireland DAC
One Warrington Place
Dublin 2, D02 HH27, Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1843/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Ordspono 2 mg concentrate for solution for infusion (sterile concentrate)
odronextamab
IV after dilution

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

2 mg/1 mL

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Ordspono 80 mg concentrate for solution for infusion
odronextamab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 80 mg odronextamab in 4 mL at a concentration of 20 mg/mL.

3. LIST OF EXCIPIENTS

Excipients: L-histidine, L-histidine monohydrochloride monohydrate, sucrose, polysorbate 80, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

concentrate for solution for infusion

80 mg/4 mL

1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For single use only
Read the package leaflet before use
For intravenous use after dilution

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not shake the vial

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keep the vial in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Regeneron Ireland DAC
One Warrington Place
Dublin 2, D02 HH27, Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1843/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Ordspono 80 mg concentrate for solution for infusion (sterile concentrate)
odronextamab
IV after dilution

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

80 mg/4 mL

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Ordspono 320 mg concentrate for solution for infusion
odronextamab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 320 mg odronextamab in 16 mL at a concentration of 20 mg/mL.

3. LIST OF EXCIPIENTS

Excipients: L-histidine, L-histidine monohydrochloride monohydrate, sucrose, polysorbate 80, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

concentrate for solution for infusion

320 mg/16 mL

1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For single use only
Read the package leaflet before use
For intravenous use after dilution

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not shake the vial

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keep the vial in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Regeneron Ireland DAC
One Warrington Place
Dublin 2, D02 HH27, Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1843/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Ordspono 320 mg concentrate for solution for infusion (sterile concentrate)
odronextamab
IV after dilution

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

320 mg/16 mL

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON THE PACKAGE SPACER IN THE FORM OF A PAPER BOOKLET PACKED IN THE OUTER CARTON

6. OTHER

Package Spacer

These pages are intentionally left blank.
The printed Package Leaflet is included in the carton.

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Ordspono 2 mg concentrate for solution for infusion
Ordspono 80 mg concentrate for solution for infusion
Ordspono 320 mg concentrate for solution for infusion

odronextamab

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- Your doctor will give you a Patient Card. Read it carefully and follow the instructions on it. Keep this Patient Card with you at all times.
- Always show the Patient Card to the doctor or nurse when you see them or if you go to hospital.
- If you have any further questions, ask your doctor, pharmacist, or nurse.
- If you get any side effects, talk to your doctor, pharmacist, or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Ordspono is and what it is used for

Ordspono is a type of antibody that is a cancer medicine. Ordspono contains the active substance odronextamab.

Ordspono is used in adults to treat the following blood cancers:

- Follicular lymphoma (FL)
- Diffuse large B-cell lymphoma (DLBCL)

In FL and DLBCL, a type of white blood cells that protect you from infection called ‘B cells’ become cancerous. The abnormal B cells do not work properly and grow too quickly. These cancerous B cells crowd out the normal B cells in the bone marrow and lymph nodes.

Ordspono is given to patients who have already tried at least two previous treatments for FL or DLBCL, when either the cancer has not responded to them (refractory), or it has come back again (relapsed).

How Ordspono works

The active substance in Ordspono, odronextamab, is a bispecific monoclonal antibody. This is a type of protein that attaches to two specific targets in the body.

- In this case, odronextamab attaches to a target substance found on B cells, including the cancerous 'B cells,' and another target found on 'T cells', a different type of white blood cell.
- T cells are another part of the body's defences that can destroy invading cells.
- By attaching T cells and B cells together like a bridge, Ordspono encourages the T cells to destroy the cancerous B cells.
- This helps control the FL and DLBCL and prevent their spread.

2. What you need to know before you are given Ordspono

You must not be given Ordspono
- if you are allergic to odronextamab or any of the other ingredients of this medicine (listed in section 6).

If you think you may be allergic, or you are not sure, talk to your doctor or nurse before you are given Ordspono.

Warnings and precautions

Talk to your doctor or nurse before you are given Ordspono if you:
- have ever had heart, lung, liver, or kidney problems
- have an infection or have had an infection in the past that lasted a long time or keeps coming back. An infection should be treated before you receive Ordspono.
- recently had a vaccine or are due to have a vaccine in the near future. Certain vaccines should not be given while you are receiving treatment with Ordspono.

If any of the above apply to you, or you are not sure, talk to your doctor or nurse before you are given Ordspono.

Tell your doctor straight away if you get signs or symptoms of any of the side effects listed below during or after treatment with Ordspono. You may need immediate medical treatment. The most common signs or symptoms of each side effect are listed in section 4 under 'Serious side effects.'

- **Cytokine release syndrome (CRS)** – a condition that can happen with medicines that stimulate T cells. CRS can be life-threatening.
  - Signs or symptoms of CRS may include fever, feeling dizzy or lightheaded, and difficulty breathing.
  - You may be given medicines that help reduce possible side effects of CRS before or after certain infusions.
  - Your doctor will monitor how your treatment is working and ask you 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.
- **Infections** – you may get signs or symptoms of infection (for example, a fever, chills, cough, or pain in urination), including life-threatening infections that may lead to death.
  - The signs and symptoms of infections can vary depending on where in the body the infection is.
  - Your doctor may prescribe another medicine to prevent certain types of infection while you are receiving Ordspono.
- **Effects on your nervous system** – you may get signs or symptoms that can include confusion or problems with the use of language.
- **Tumour lysis syndrome –**some people may get unusual levels of some salts (such as potassium and uric acid) in the blood – caused by the fast breakdown of cancer cells during treatment.
  - Your doctor or nurse will do blood tests to check for this condition.
  - Before each infusion with Ordspono, you should be well-hydrated and may be given medicines that can help reduce high levels of uric acid.

- These measures may help reduce possible side effects of tumour lysis syndrome.
- **Lung inflammation (pneumonitis/interstitial lung disease) –** you may get signs or symptoms that can include new or worsening cough, being short of breath

Children and adolescents

Ordspono should not be used in children and adolescents below 18 years of age because Ordspono has not been studied in this age group.

Other medicines and Ordspono

Tell your doctor if you are taking, have recently taken, or might take any other medicines. This includes medicines obtained without a prescription and herbal medicines.

Pregnancy

It is important to tell your doctor before and during treatment if you are pregnant, think you may be pregnant, or are planning to get pregnant. Ordspono is not recommended during pregnancy and in women who can get pregnant and are not using contraception. Ordspono may harm your unborn baby.

Contraception

Women who could become pregnant must use effective contraception during treatment - and for 6 months after the last dose of Ordspono.

Breast-feeding

You must not breast-feed during and for at least 6 months after your last treatment with Ordspono. This is because it is not known whether any Ordspono passes into breast milk and could therefore harm the baby.

Driving and using machines

Ordspono has minor influence on your ability to drive, cycle or use any tools or machines. Some people may feel tired, dizzy, light-headed, or confused while taking Ordspono. If you feel any symptoms that may affect your ability to drive, do not drive or use tools or machines until your symptoms go away. See section 4 for more information about side effects.

3. How Ordspono is given

Ordspono is given under the supervision of a doctor experienced in giving such treatments. Follow the treatment schedule explained to you by your doctor. Check with your doctor if you are not sure.

How Ordspono is given

Ordspono is given into a vein, as a drip (intravenous infusion).
- For Cycles 1, 2, 3, and 4, a treatment cycle is 21 days.
- Ordspono is given over 4 hours during Cycle 1 and on Cycle 2, Day 1.
- The next doses may be given over 1 hour if side effects are not too severe.
- After Cycle 4, you will get a maintenance dose every 2 weeks.

Medicines given before and after treatment with Ordspono

You will be given other medicines before and after treatment with Ordspono in Cycle 1 and Cycle 2, Days 1 and 8. These medicines help reduce the risk of CRS and infusion-related reactions (IRR). These medicines may include:

- Corticosteroids – such as dexamethasone
- Paracetamol
- An antihistamine - such as diphenhydramine

After Cycle 2 Day 8, your doctor will decide if you need to continue to take other medicines to help reduce side effects from Ordspono during future cycles.

How much Ordspono is given

For the treatment of follicular lymphoma (FL) and diffuse large B-cell lymphoma (DLBCL), a treatment cycle of Ordspono from Cycles 1, 2, 3, and 4 is 21 days.

In Cycle 1, you will be given increasing doses of Ordspono to treat FL or DLBCL on the following days:

- Day 1: 0.2 mg
- Day 2: 0.5 mg
- Day 8: 2 mg
- Day 9: 2 mg
- Day 15: 10 mg
- Day 16: 10 mg

In Cycles 2, 3, and 4, you will be given a dose on Days 1, 8, and 15:

- for follicular lymphoma: 80 mg
- for diffuse large B-cell lymphoma: 160 mg

If your dose of Ordspono is delayed for any reason, you may need to restart treatment from Cycle 1.

One week after the end of Cycle 4, you will be given a maintenance dose every 2 weeks.
The maintenance doses are as follows:

- for follicular lymphoma: 160 mg
- for diffuse large B-cell lymphoma: 320 mg

If your cancer has been in remission for at least 9 months, your doctor may decide to reduce your dosing frequency from every 2 weeks to every 4 weeks.

Your doctor may continue your treatment for as long as you continue to respond to Ordspono or for as long as side effects are not too severe. Your doctor may delay or completely stop your treatment with Ordspono if you have certain side effects.

If you miss an appointment

If you miss an appointment, make another one straight away. For the treatment to be fully effective, it is very important not to miss a dose.

If you stop receiving Ordspono

Do not stop treatment with Ordspono unless you have discussed this with your doctor. This is because stopping your treatment may make your condition worse.

If you have any further questions on the use of this medicine, ask your doctor or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. These side effects may happen any time during treatment or even after your treatment has ended.

Serious side effects
Tell your doctor straight away if you notice any symptoms of the following serious side effects. You may only get one or some of these symptoms.

Cytokine release syndrome (**very common:** may affect more than 1 in 10 people)
Signs and symptoms can include:
- fever (38°C or higher)
- feeling dizzy or lightheaded
- fast or irregular heartbeat
- difficulty breathing
- chills or shaking
- headache

Infections (**very common:** may affect more than 1 in 10 people)
Signs and symptoms can include:
- fever (38°C or higher)
- chills or shaking
- cough or feeling short of breath
- sore throat
- pain when passing urine

Very common infections (may affect more than 1 in 10 people):
- COVID 19
- infection of the lungs (pneumonia)
- cytomegalovirus infection, which can cause serious complications in people whose immune system is compromised
- infection of the nose and throat (upper respiratory tract infection)
- infection of the parts of the body that collect and pass urine (urinary tract infection)
- herpes virus infection

Common infections (may affect up to 1 in 10 people):
- airway (respiratory tract) infection
- fungal infection
- inflammation of the sinuses (sinusitis)
- blood poisoning (sepsis)
- bacteria in the blood (bacteraemia)

Effects on your nervous system (**uncommon**: may affect up to 1 in 100 people)
Signs and symptoms can include:
- headache
- dizziness
- decreased brain function, such as trouble thinking
- feeling anxious
- feeling confused

Tumour lysis syndrome (**uncommon**: may affect up to 1 in 100 people)

Signs and symptoms can include:
- weakness
- shortness of breath
- feeling confused
- irregular heartbeat
- muscle cramps

Lung inflammation (pneumonitis/interstitial lung disease) (**common**: may affect up to 1 in 10 people)
Signs and symptoms can include:
- being short of breath
- new or worsening cough

If you have any of these signs or symptoms during or after treatment with Ordspono, tell your doctor straight away. You may need medical treatment.

Other side effects
Other side effects are listed below. Tell your doctor or nurse if you get any of these side effects.

Very common (may affect more than 1 in 10 people):
- Fever (pyrexia)
- Muscle pain or bone (musculoskeletal) pain
- Feeling tired (fatigue)
- Diarrhoea
- Rash
- Cough
- Swollen hands, ankles, or feet (oedema)
- Feeling sick (nausea)
- Stomach pain (abdominal pain)
- Constipation
- Infusion-related reactions (IRR)
- Feeling less hungry (decreased appetite)
- Difficulty falling or staying asleep (insomnia)
- Low blood pressure (hypotension)
- Headache
- Feeling short of breath at rest or with activity (dyspnoea)
- Vomiting

Shown in blood tests
- Low number of red blood cells (anaemia) that can make you feel tired or short of breath
- Low levels of some types of white blood cells (neutropenia, leukopenia, lymphopenia), which can increase the risk for infection
- Low platelet count (thrombocytopenia) that may make you more likely to bruise or bleed
- Low level of potassium, sodium, or phosphate (hypokalaemia, hyponatremia, or hypophosphataemia)
- High level of sugar in the blood (hyperglycaemia)
- High level of alanine aminotransferase or aspartate aminotransferase in the blood

Common (may affect up to 1 in 10 people):
- Fast or uneven heartbeat (tachycardia)
- Weakness, numbness, and pain, usually in the hands and feet (neuropathy peripheral)
- Confusion, disorientation, sleepiness (mental status changes)

- condition that can cause inflammation of lung tissue that can affect your ability to breathe (interstitial lung disease)
- fever due to low levels of neutrophils (a type of white blood cell)

Shown in blood tests
- High level of gamma-glutamyltransferase, an enzyme found mostly in the liver
- Low level of magnesium (hypomagnesaemia)
- Low level of albumin (hypoalbuminaemia)
- Increased levels of bilirubin, which may cause yellowing of skin or eyes, and dark urine

Uncommon (may affect up to 1 in 100 people):
- Difficulty with speech (aphasia)
- A rapid breakdown of tumour cells called tumour lysis syndrome. This can cause chemical changes in the blood and damage to organs, including the kidneys, heart, and liver
- Effects on your nervous system with symptoms that can include feeling confused or less alert (immune effector cell-associated neurotoxicity syndrome or neurotoxicity)

Reporting of side effects
If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Ordspono

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and vial after EXP. The expiry date refers to the last day of that month.

Ordspono will be stored by healthcare professionals at the hospital or clinic. This storage information is for their use.

Unopened vial

Store in a refrigerator (2 °C to 8 °C).

Do not freeze.

Keep the vial in the outer carton in order to protect from light.

Diluted solution

Chemical and physical in-use stability has been demonstrated for the diluted Ordspono infusion solution as follows:
- in a refrigerator (2 °C to 8 °C) for all doses for up to 24 hours.
- at room temperature (20 °C to 25 °C) for up to 6 hours for the 0.2-mg dose with Albumin (Human).
- at room temperature (20 °C to 25 °C) for up to 12 hours for doses of 0.5 mg or greater.

Discard diluted infusion solution if storage time exceeds these limits.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 °C to 8 °C, unless dilution has taken place in controlled and validated aseptic conditions.

Your doctor will dispose of any unneeded medicine appropriately. These measures will help protect the environment.

6. Contents of the pack and other information

What Ordspono contains

The active substance is odronextamab.

- Ordspono 2 mg: Each vial contains 2 mg of odronextamab (in 1 mL concentrate) at a concentration of 2 mg/1 mL.
- Ordspono 80 mg: Each vial contains 80 mg of odronextamab (in 4 mL concentrate) at a concentration of 20 mg/1 mL.
- Ordspono 320 mg: Each vial contains 320 mg of odronextamab (in 16 mL concentrate) at a concentration of 20 mg/1 mL.

The other ingredients are L-histidine, L-histidine monohydrochloride monohydrate, sucrose, polysorbate 80 (E433), and water for injections.

What Ordspono looks like and contents of the pack

Ordspono concentrate for solution (sterile concentrate) for infusion is supplied as a clear to slightly opalescent, colourless to pale yellow solution provided in a glass vial.

Each pack contains one vial.

Marketing Authorisation Holder
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Manufacturer
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Raheen Business Park
Limerick
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This leaflet was last revised in

This medicine has been given ‘conditional approval’. This means that there is more evidence to come about this medicine. The European Medicines Agency will review new information on this medicine at least every year and this leaflet will be updated as necessary.

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu

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The following information is intended for healthcare professionals only:

Procedures for proper handling and disposal of anticancer medicinal products should be considered.

Instructions for dilution

General precautions

Proper aseptic technique throughout the handling of this medicinal product should be followed. Ordspono contains no preservative and is intended for single-dose only. Discard any unused portion left in the vial. Do not shake.

Nature and contents of container

2 mg concentrate for solution for infusion

1 mL of concentrate for solution for infusion in a 2 mL Type I clear glass vial with a grey chlorobutyl stopper with coating and an aluminium seal cap with a dark blue flip-off button containing 2 mg of odronextamab.

Pack of one vial.

80 mg concentrate for solution for infusion

4 mL of concentrate for solution for infusion in a 10 mL Type I clear glass vial with a grey chlorobutyl stopper with coating and an aluminium seal cap with a light green flip-off button containing 80 mg of odronextamab.

Pack of one vial.

320 mg concentrate for solution for infusion

16 mL of concentrate for solution for infusion in a 20 mL Type I clear glass vial with a grey chlorobutyl stopper with coating and an aluminium seal cap with a white flip-off button containing 320 mg of odronextamab.

Pack of one vial.

Instructions for dilution

Visually inspect for particulate matter and discoloration prior to administration. Ordspono is a clear to slightly opalescent, colourless to pale yellow solution. Discard the vial if the solution is cloudy, discoloured, or contains particulate matter.

Preparation of 0.2-mg dose

- Prepare Albumin (Human) in sodium chloride 9 mg/mL (0.9%) solution for injection in a 100-mL intravenous bag [polyvinyl chloride (PVC) or polyolefin (PO)] as per Table 1 below.
  - **Note:** Albumin (Human) is only required for the 0.2-mg dose to prevent adsorption of odronextamab to the intravenous filter. When Albumin (Human) is used, please see Traceability in section 4.4.
- The final Albumin (Human) concentration should be 0.04%.

Table 1: Examples of Albumin (Human) concentration and volumes required for the 0.2-mg dose

Albumin (Human) concentration[a]	Albumin (Human) volume for addition to a 100 mL sodium chloride 9 mg/mL (0.9%) solution for injection, infusion bag
5%	0.8 mL
20%	0.2 mL
25%	0.16 mL
[a] Albumin (Human): use concentration as per local availability. Examples include but are not restricted to the following strengths: 5%, 20%, or 25%.	

- Mix the Albumin (Human) and sodium chloride 9 mg/mL (0.9%) solution for injection by gentle inversion. Do not shake.
- Obtain 1 vial of 2 mg Ordspono.
- Withdraw 0.1 mL from the 2-mg Ordspono vial using a 1-mL syringe and add into the prepared 100-mL intravenous bag.
- Mix diluted solution by gentle inversion. Do not shake.

Preparation of 0.5-mg dose

- Obtain a 50-mL intravenous bag (PVC or PO) containing sodium chloride 9 mg/mL (0.9%) solution for injection.
- Obtain 1 vial of 2 mg Ordspono.
- Withdraw 0.25 mL from the 2-mg Ordspono vial using a 1-mL syringe and add into the 50-mL intravenous bag.
- Mix diluted solution by gentle inversion. Do not shake.

Preparation of 1-mg or above dose

- Obtain a 50- or 100-mL intravenous bag (PVC or PO) containing sodium chloride 9 mg/mL (0.9%) solution for injection.
- Obtain the required number of vials and withdraw the appropriate volume of Ordspono.
  - Refer to Table 2 for the specific volume for the intended dose.
  - Refer to Table 3 for the specific volume for dose modifications (see section 4.2 of the SmPC).
- Add the appropriate volume of Ordspono to the intravenous bag.
- Mix diluted solution by gentle inversion. Do not shake.

Summary tables for dilution prior to administration

Table 2: Ordspono volumes for addition to the infusion bag (standard doses)

Ordspono dose (mg)	Amount of Ordspono per vial (mg)	Concentration of vial (mg/mL)	Total volume of Ordspono to prepare dose (mL)	Albumin (Human) required	Sodium chloride 9 mg/mL (0.9%) solution for injection, infusion bag (PO or PVC) volume (mL)
0.2	2	2	0.1	Yes	100
0.5	2	2	0.25	No	50
2	2	2	1	No	50 or 100
10	2	2	5	No	50 or 100

Ordspono dose (mg)	Amount of Ordspono per vial (mg)	Concentration of vial (mg/mL)	Total volume of Ordspono to prepare dose (mL)	Albumin (Human) required	Sodium chloride 9 mg/mL (0.9%) solution for injection, infusion bag (PO or PVC) volume (mL)
80	80	20	4	No	50 or 100
160	80	20	8	No	50 or 100
320	320	20	16	No	50 or 100

Table 3: Other Ordspono volumes for addition to the infusion bag for dose modifications

Ordspono dose (mg)	Amount of Ordspono per vial (mg)	Concentration of vial (mg/mL)	Total volume of Ordspono (mL)	Albumin (Human) required	Sodium chloride 9 mg/mL (0.9%) solution for injection, infusion bag (PO or PVC) volume (mL)
1	2	2	0.5	No	50 or 100
5	2	2	2.5	No	50 or 100
40	80	20	2	No	50 or 100

For storage conditions of the diluted solution in infusion bags, see Storage below.

Method of administration

Ordspono is for intravenous use after dilution only. Ordspono must be diluted using aseptic technique.

- The first cycle of Ordspono is administered as a 4-hour infusion. If Ordspono is tolerated on Cycle 2, Day 1, infusion time can be reduced to 1 hour for all subsequent doses.
- Ordspono must not be administered as intravenous push or bolus.
- See Table 1 for premedications and post-medications.
- For doses that are not tolerated, refer to Tables 4, 5, and 6 for management guidance.

After Ordspono has been diluted as instructed above, administer as follows:

- Connect the prepared intravenous infusion bag containing the final Ordspono solution to intravenous tubing constructed of polyvinyl chloride (PVC), polyethylene (PE)-lined PVC, or polyurethane (PU). It is recommended to use a 0.2-micron or 5-micron polyethersulfone (PES) filter.
- Prime with Ordspono to the end of the intravenous tubing.
- Do not mix Ordspono with other medicinal products or concurrently administer other medicinal products through the same intravenous line.
- Upon completion of Ordspono infusion, flush the infusion line with adequate volume of sodium chloride 9 mg/mL (0.9%) solution for injection to ensure that the entire contents of the infusion bag are administered.

Storage

Unopened vial

Store in a refrigerator (2 °C to 8 °C).
Do not freeze.
Keep the vial in the original outer carton in order to protect from light.

Storage of diluted solution

Chemical and physical in-use stability has been demonstrated for the diluted Ordspono infusion solution as follows:

- in a refrigerator (2 °C to 8 °C) for all doses for up to 24 hours.
- at room temperature (20 °C to 25 °C) for up to 6 hours for the 0.2-mg dose with Albumin (Human).
- at room temperature (20 °C to 25 °C) for up to 12 hours for doses of 0.5 mg or greater.

Discard diluted infusion solution if storage time exceeds these limits.

Disposal

The release of pharmaceuticals into the environment should be minimised. Medicinal products should not be disposed of via wastewater and disposal through household waste should be avoided.

The following points should be strictly adhered to regarding the use and disposal of syringes and other medicinal sharps:

- Needles and syringes should never be reused.
- Place all used needles and syringes into a sharps container (puncture-proof disposable container).

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

ANNEX IV

CONCLUSIONS ON THE GRANTING OF THE CONDITIONAL MARKETING AUTHORISATION PRESENTED BY THE EUROPEAN MEDICINES AGENCY

Conclusions presented by the European Medicines Agency on:

- **Conditional marketing authorization**

The CHMP having considered the application is of the opinion that the risk-benefit balance is favourable to recommend the granting of the conditional marketing authorisation as further explained in the European Public Assessment Report.