SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Tepkinly 4 mg/0.8 ml solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 0.8 ml single use vial contains 4 mg of epcoritamab at a concentration of 5 mg/ml.

Epcoritamab is a humanised immunoglobulin G1 (IgG1)-bispecific antibody against CD3 and CD20 antigens, produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology.

Excipient with known effect
Each vial of Tepkinly contains 21.9 mg of sorbitol and 0.42 mg polysorbate 80.
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection (injection)

Colourless to slightly yellow solution, pH 5.5 and osmolarity of approximately 211 mOsm/kg.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

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

4.2 Posology and method of administration

Tepkinly must only be administered under the supervision of a healthcare professional qualified in the use of anti-cancer therapies, with access to appropriate medical support to manage severe reactions such as cytokine release syndrome (CRS) (see section 4.4).

Posology

Recommended pre-medication and dose schedule

Details on recommended premedication for cytokine release syndrome (CRS) are shown in Table 1.

Table 1 – Epcoritamab premedication and CRS prophylaxis

Cycle	**Patient requiring premedication**	**Premedication**	**Corticosteroid prophylaxis**
Cycle 1	All patients	30-120 minutes prior to each weekly administration of epcoritamab • Dexamethasone[b] (15 mg oral or intravenous) or Prednisolone (100 mg oral or IV) or equivalent • Diphenhydramine (50 mg oral or IV) or equivalent • Paracetamol (1000 mg oral)	Prednisolone (100 mg oral or IV) or equivalent for three consecutive days following each weekly administration of epcoritamab in Cycle 1
Cycle 2 and beyond	Patients who experienced Grade 2 or 3[a] CRS with previous dose	30-120 minutes prior to next administration of epcoritamab after a grade 2 or 3[a] CRS event • Dexamethasone[b] (15 mg oral or intravenous) or Prednisolone (100 mg oral or IV) or equivalent	Prednisolone (100 mg oral or IV) or equivalent for three consecutive days following the next administration of epcoritamab until epcoritamab is given without subsequent CRS of any grade

[a] Patients will be permanently discontinued from epcoritamab after a Grade 4 CRS event.
[b]Dexamethasone is the preferred corticosteroid for CRS prophylaxis based on the GCT3013-01 Optimisation study.

Administer Tepkinly according to the step-up dose schedule in 28-day cycles outlined in Table 2 for patients with diffuse large B-cell lymphoma and Table 3 for patients with follicular lymphoma.

Tepkinly is for subcutaneous (SC) injection only.

Table 2 - Tepkinly 2-step step-up dose schedule for patients with diffuse large B-cell lymphoma

Dosing schedule	**Cycle of treatment**	**Days**	**Epcoritamab dose (mg)[a]**
Weekly	Cycle 1	1	0.16 mg (Step-up dose 1)
		8	0.8 mg (Step-up dose 2)
		15	48 mg (First full dose)
		22	48 mg
Weekly	Cycles 2 - 3	1, 8, 15, 22	48 mg
Every two weeks	Cycles 4 - 9	1, 15	48 mg
Every four weeks	Cycles 10 +	1	48 mg
[a]0.16 mg is a priming dose, 0.8 mg is an intermediate dose and 48 mg is a full dose.			

Table 3 - Tepkinly 3-step step-up dose schedule for patients with follicular lymphoma

Dosing schedule	**Cycle of treatment**	**Days**	**Epcoritamab dose (mg)[a]**
Weekly	Cycle 1	1	0.16 mg (Step-up dose 1)
		8	0.8 mg (Step-up dose 2)
		15	3 mg (Step-up dose 3)
		22	48 mg (First full dose)
Weekly	Cycles 2 - 3	1, 8, 15, 22	48 mg
Every two weeks	Cycles 4 - 9	1, 15	48 mg
Every four weeks	Cycles 10 +	1	48 mg
[a]0.16 mg is a priming dose, 0.8 mg is an intermediate dose, 3 mg is a second intermediate dose and 48 mg is a full dose.			

Tepkinly should be administered until disease progression or unacceptable toxicity. Atypical responses (i.e. an initial transient increase in tumour size or small new lesions within the first few months followed by tumour shrinkage) have been observed. It is recommended to continue treatment for clinically stable patients with initial evidence of disease progression until disease progression is confirmed.

Tepkinly should be administered to well hydrated patients.

Prophylaxis against *Pneumocystis jirovecii* pneumonia (PCP) and herpes virus infections is strongly recommended especially during concurrent use of steroids.

It is strongly recommended that all patients adhere to the following fluid guidelines during Cycle 1, unless medically contraindicated:

- 2-3 L of fluid intake during the 24 hours prior to each epcoritamab administration
- Hold antihypertensive medications for 24 hours prior to each epcoritamab administration
- Administer 500 ml isotonic intravenous (IV) fluids on the day of epcoritamab prior to dose administration; AND
- 2-3 L of fluid intake during the 24 hours following each epcoritamab administration.

Patients at an increased risk for clinical tumour lysis syndrome (CTLS) are recommended to receive hydration and prophylactic treatment with a uric acid lowering agent.

Monitor patients for potential CRS and/or immune effector cell-associated neurotoxicity syndrome (ICANS) and managed per current practice guidelines following epcoritamab administration (see section 4.4).

Missed or delayed dose

Diffuse large B-cell lymphoma
A re-priming cycle (identical to Cycle 1 with standard CRS prophylaxis) is required:

- If there are more than 8 days between the priming dose (0.16 mg) and intermediate dose (0.8 mg), or
- If there are more than 14 days between the intermediate dose (0.8 mg) and first full dose (48 mg), or
- If there are more than 6 weeks between full doses (48 mg)

After the re-priming cycle, the patient should resume treatment with Day 1 of the next planned treatment cycle (subsequent to the cycle during which the dose was delayed).

Follicular lymphoma
A re-priming Cycle (identical to Cycle 1 with standard CRS prophylaxis) is required:

- If there are more than 8 days between the priming dose (0.16 mg) and intermediate dose (0.8 mg), or
- If there are more than 8 days between the intermediate dose (0.8 mg) and the second intermediate dose (3 mg), or
- If there are more than 14 days between the second intermediate dose (3 mg) and first full dose (48 mg), or
- If there are more than 6 weeks between any two full doses (48 mg)

After the re-priming cycle, the patient should resume treatment with Day 1 of the next planned treatment cycle (subsequent to the cycle during which the dose was delayed).

Dosage modifications and management of adverse reactions

Cytokine release syndrome (CRS)
Patients treated with epcoritamab may develop CRS.
Evaluate for and treat other causes of fever, hypoxia, and hypotension. If CRS is suspected, manage according to the recommendations in Table 4. Patients who experience CRS should be monitored more frequently during next scheduled epcoritamab administration.

Table 4 - CRS grading and management guidance

Grade[1]	**Recommended therapy**	**Epcoritamab dose modification**
Grade 1 **• Fever (temperature ≥ 38°C) without hypotension or hypoxia**	Provide supportive care such as antipyretics and intravenous hydration **Anti-cytokine therapy:** Consider anti-cytokine therapy in certain cases, e.g., advanced age, high tumour burden, circulating tumour cells, fever refractory to antipyretics. Tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg per dose). Repeat tocilizumab after at least 8 hours as needed. Maximum of 2 doses in a 24-hour period. In case of concurrent ICANS choose alternative to tocilizumab. See **Table 5.** **Corticosteroids** In case of concurrent ICANS, initiation of corticosteroids is highly recommended. Consider dexamethasone 10-20 mg per day (or equivalent).	Hold epcoritamab until resolution of CRS event

Grade[1]	Recommended therapy	Epcoritamab dose modification
Grade 2[a] **• Fever (temperature ≥ 38°C)** **AND/OR** **• Hypotension not requiring vasopressors** **AND/OR** **• Hypoxia requiring low-flow (≤6 l/minute) nasal cannula or blow-by**	Provide supportive care such as antipyretics and intravenous hydration **Anti-cytokine therapy:** Tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg per dose). Repeat tocilizumab after at least 8 hours as needed. Maximum of 2 doses in a 24-hour period. If CRS is refractory to initial anti-cytokine therapy, initiate/increase dose of corticosteroid therapy and consider alternative anti-cytokine therapy. In case of concurrent ICANS choose alternative to tocilizumab. See **Table 5.** **Corticosteroids:** In case of concurrent ICANS, initiation of corticosteroids is highly recommended. Consider dexamethasone 10-20 mg per day (or equivalent).	Hold epcoritamab until resolution of CRS event.
Grade 3[a] **• Fever (temperature ≥ 38°C)** **AND/OR** **• Hypotension requiring 1 vasopressor with or without vasopressin** **AND/OR** **• Hypoxia requiring high-flow (>6 l/minute) nasal cannula, facemask, non-rebreather mask, or venturi mask**	Provide supportive care such as antipyretics and intravenous hydration **Anti-cytokine therapy** Tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg per dose). Repeat tocilizumab after at least 8 hours as needed. Maximum of 2 doses in a 24-hour period. If CRS is refractory to initial anti-cytokine therapy, initiate/increase dose of corticosteroid therapy and consider alternative anti-cytokine therapy.	Hold epcoritamab until resolution of CRS event. In the event of Grade 3 CRS lasting longer than 72 hours, epcoritamab should be discontinued. If more than 2 separate events of Grade 3 CRS, even if each event resolved to Grade 2 within 72 hours, epcoritamab should be discontinued.

Grade[1]	Recommended therapy	Epcoritamab dose modification
	In case of concurrent ICANS choose alternative to tocilizumab. See **Table 5.** **Corticosteroids:** Dexamethasone (e.g., 10-20 mg IV every 6 hours). If no response, initiate methylprednisolone 1000 mg/day.	
Grade 4 **• Fever (temperature ≥ 38°C)** **AND/OR** **• Hypotension requiring ≥ 2 vasopressors (excluding vasopressin)** **AND/OR** **• Hypoxia requiring positive pressure ventilation (e.g., CPAP, BiPAP, intubation and mechanical ventilation)**	Provide supportive care such as antipyretics and intravenous hydration **Anti-cytokine therapy** Tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg per dose). Repeat tocilizumab after at least 8 hours as needed. Maximum of 2 doses in a 24-hour period. If CRS is refractory to initial anti-cytokine therapy, initiate/increase dose of corticosteroid therapy and consider alternative anti-cytokine therapy. In case of concurrent ICANS choose alternative to tocilizumab See **Table 5.** **Corticosteroids** Dexamethasone (e.g., 10-20 mg IV every 6 hours). If no response, initiate methylprednisolone 1000 mg/day.	Permanently discontinue epcoritamab
[1] CRS graded according to ASTCT (American Society for Transplant and Cellular Therapy) consensus criteria (Lee et al., 2019) **[a] If Grade 2 or 3 CRS occurs with the second full dose or beyond, administer CRS prophylaxis with each subsequent dose until epcoritamab dose is given without subsequent CRS (of any grade).**		

Immune effector cell associated neurotoxicity syndrome (ICANS)

Monitor patients for signs and symptoms of ICANS. Rule out other causes of neurologic symptoms. If ICANS is suspected, manage according to the recommendations in Table 5.

Table 5 - ICANS grading and management guidance

Grade[a]	**Recommended therapy**	**Epcoritamab dose modification**
Grade 1[b] **ICE score**[c] **7-9**[b] **or, depressed level of consciousness**[b]**: awakens spontaneously.**	Dexamethasone, 10 mg IV every 12 hours Consider non-sedating anti-seizure medication (e.g., levetiracetam) until resolution of ICANS. No concurrent CRS: • Anti-cytokine therapy not recommended For ICANS with concurrent CRS: • Treatment with dexamethasone[d] • Choose immunosuppressant alternatives[e] to tocilizumab, if possible	Hold epcoritamab until resolution of event.
Grade 2[b] **ICE score**[c] **3-6** **or, depressed level of consciousness**[b]**: awakens to voice.**	Dexamethasone at 10-20 mg IV every 12 hours Consider non-sedating anti-seizure medication (e.g., levetiracetam) until resolution of ICANS. No concurrent CRS: • Anti-cytokine therapy not recommended For ICANS with concurrent CRS: • Treatment with dexamethasone[d] • Choose immunosuppressant alternatives[e] to tocilizumab, if possible	Hold epcoritamab until resolution of event.
Grade 3[b] **ICE score**[c] **0-2** **or, depressed level of consciousness**[b]**: awakens only to tactile stimulus, or** **seizures**[b]**, either:**	Dexamethasone 10-20 mg IV every 6 hours. • If no response, initiate methylprednisolone 1000 mg/day. Consider non-sedating anti-seizure medication (e.g., levetiracetam) until resolution of ICANS. No concurrent CRS:	**First episode*:*** delay epcoritamab until full resolution of event. **Second episode:** permanently discontinue

Grade[a]	Recommended therapy	Epcoritamab dose modification
• **any clinical seizure, focal or generalized that resolves rapidly,** **or** • **non-convulsive seizures on electroencephalogram (EEG) that resolve with intervention,** **or** **raised intracranial pressure: focal/local oedema[b] on neuroimaging[c]**	• Anti-cytokine therapy not recommended For ICANS with concurrent CRS: • Treatment with dexamethasone o If no response, initiate methylprednisolone 1000 mg/day • Choose immunosuppressant alternatives[e] to tocilizumab, if possible	epcoritamab.
Grade 4[b] **ICE score[c, b] 0** **or, depressed level of consciousness[b] either:** • **patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse, or** • **stupor or coma, or** **seizures[b], either:** • **life-threatening prolonged seizure (>5 minutes), or** • **repetitive clinical or electrical seizures without return to baseline in between,** **or** **motor findings[b]:** • **deep focal motor weakness such as**	Dexamethasone 10-20 mg IV every 6 hours. • If no response, initiate methylprednisolone 1000 mg/day. Consider non-sedating anti-seizure medication (e.g., levetiracetam) until resolution of ICANS. No concurrent CRS: • Anti-cytokine therapy not recommended For ICANS with concurrent CRS: • Treatment with dexamethasone o If no response, initiate methylprednisolone 1000 mg/day • Choose immunosuppressant alternatives[e] to tocilizumab, if possible	Permanently discontinue epcoritamab.

Grade[a]	Recommended therapy	Epcoritamab dose modification
hemiparesis or paraparesis, or **raised intracranial pressure / cerebral oedema[b], 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] ICANS graded according to ASTCT ICANS Consensus Grading (Lee et al., 2019)
[b] ICANS grade is determined by the most severe event (ICE score, level of consciousness, seizures, motor findings, raised ICP/cerebral edema) not attributable to any other cause
[c] If patient is arousable and able to perform Immune Effector Cell-Associated Encephalopathy (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] Dexamethasone should be administered at 10 mg intravenously every 12 hours
[e] Riegler L et al. (2019)

Table 6: Recommended Dosage Modifications for Other Adverse Reactions

Adverse Reaction[1]	Severity[1]	Action
Infections (*see section 4.4)*	Grades 1-4	Withhold epcoritamab in patients with active infection, until the infection resolves
Febrile neutropenia	Absolute neutrophil count less than 0.5×10^9/L	Withhold epcoritamab until absolute neutrophil count is 0.5×10^9/L or higher
Thrombocytopenia *(see section 4.8)*	Platelet count less than 50×10^9/L	Withhold epcoritamab until

		platelet count is 50 x 10^9/L or higher
Other Adverse Reactions *(see section 4.8)*	Grade 3 or higher	Withhold epcoritamab until the toxicity resolves to Grade 1 or baseline
[1] Based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 5.0.		

Special populations

Renal impairment

No formal studies of Tepkinly in patients with renal impairment have been conducted. Based on population pharmacokinetic (PK) analyses, no dosage adjustment is necessary for patients with mild or moderate renal impairment. No data are available in patients with severe renal impairment (see section 5.2).

Hepatic impairment

No formal studies of Tepkinly in patients with hepatic impairment have been conducted. Based on population pharmacokinetic (PK) analyses, no dosage adjustment is necessary for patients with mild hepatic impairment. Data are limited in patients with moderate hepatic impairment and no data are available in patients with severe hepatic impairment (see section 5.2).

Paediatric population

The safety and efficacy of Tepkinly in children aged less than 18 years of age have not yet been established. No data are available.

Elderly

No dose adjustment is necessary in patients ≥ 65 years.

Method of administration

Tepkinly should be administered by subcutaneous injection, preferably in the lower part of the abdomen or the thigh. Change of injection site from left to right side or vice versa is recommended especially during the weekly administration schedule (i.e., Cycles 1-3).

For instructions on dilution of the medicinal product before administration, see section 6.6.

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.

Cytokine release syndrome (CRS)

Cytokine release syndrome, which may be life-threatening or fatal, occurred in patients receiving epcoritamab (see section 4.8). The most common signs and symptoms of CRS include pyrexia, hypotension and hypoxia. Other signs and symptoms of CRS include chills, tachycardia, headache and dyspnoea.

Most CRS events occurred in Cycle 1 and were associated with the first full dose of epcoritamab. Administer prophylactic corticosteroids to mitigate the risk of CRS (see section 4.2).

Patients should be monitored for signs and symptoms of CRS following epcoritamab administration.
At the first signs or symptoms of CRS, institute treatment of supportive care with tocilizumab and/or corticosteroids as appropriate (see section 4.2, Table 4). Counsel patients on the signs and symptoms associated with CRS and instruct patients to contact their healthcare professional and seek immediate medical attention should signs or symptoms occur at any time. Management of CRS may require either temporary delay or discontinuation of epcoritamab based on the severity of CRS (see section 4.2).

Patients with DLBCL should be hospitalised for 24 hours after administration of the Cycle 1 Day 15 dose of 48 mg to monitor for signs and symptoms of CRS.

Haemophagocytic lymphohistiocytosis (HLH)

Haemophagocytic lymphohistiocytosis (HLH), including fatal cases, have been reported in patients receiving epcoritamab. HLH is a life-threatening syndrome characterised by fever, skin rash, lymphadenopathy, hepato- and/or splenomegaly and cytopenias. HLH should be considered when the presentation of CRS is atypical or prolonged. Patients should be monitored for clinical signs and symptoms of HLH. For suspected HLH, epcoritamab must be interrupted for diagnostic workup and treatment for HLH initiated. If HLH is confirmed, administration of Tepkinly should be discontinued.

Immune effector cell-associated neurotoxicity syndrome (ICANS)

ICANS, including fatal events, have occurred in patients receiving epcoritamab (see section 4.8). ICANS may manifest as aphasia, altered level of consciousness, impairment of cognitive skills, motor weakness, seizures, and cerebral oedema.

The majority of cases of ICANS occurred within the Cycle 1 of epcoritamab treatment, however some occurred with delayed onset.

Patients should be monitored for signs and symptoms of ICANS following epcoritamab administration. At the first signs or symptoms of ICANS institute treatment with corticosteroids and non-sedating-anti-seizure medications as appropriate (see section 4.2, Table 5).

Patients with DLBCL should be hospitalised for 24 hours after administration of the Cycle 1 Day 15 dose of 48 mg to monitor for signs and symptoms of ICANS.

Counsel patients on the signs and symptoms of ICANS and that the onset of events may be delayed. Instruct patients to contact their healthcare professional and seek immediate medical attention should signs or symptoms occur at any time. Delay or discontinue epcoritamab as recommended (see section 4.2).

Serious infections

Serious or fatal infections were observed in patients treated with epcoritamab in clinical studies (see section 4.8).

Epcoritamab must not be administered in patients with active infections. As appropriate, administer prophylactic antimicrobials prior to and during treatment with epcoritamab (see section 4.2). Caution should be exercised when considering the use of epcoritamab in patients with a history of recurring or chronic infections, with underlying conditions that may predispose to infections or who have had significant prior immunosuppressive treatment. Patients should be monitored for signs and symptoms of infection before and after epcoritamab administration and treated appropriately. 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.

Hypogammaglobulinaemia has also been reported in patients receiving epcoritamab (see section 4.8). Immunoglobulin (Ig) levels should be monitored prior to and during treatment. Patients should be treated according to local institutional guidelines, including infection precautions and antimicrobial prophylaxis.

Cases of progressive multifocal leukoencephalopathy (PML), including fatal cases, have been reported in patients treated with epcoritamab who have also received prior treatment with other immunosuppressive medications. If neurological symptoms suggestive of PML occur during epcoritamab therapy, treatment with epcoritamab should be discontinued and appropriate diagnostic measures initiated.

Tumour Lysis Syndrome (TLS)

TLS has been reported in patients receiving epcoritamab (see section 4.8). Patients at an increased risk for TLS are recommended to receive hydration and prophylactic treatment with a uric acid lowering agent. Patients should be monitored for signs or symptoms of TLS, especially patients with high tumour burden or rapidly proliferative tumours, and patients with reduced renal function. Patients should be monitored for blood chemistries and abnormalities should be managed promptly.

Tumour flare

Tumour flare has been reported in patients treated with epcoritamab (see section 4.8). Manifestations could include localised pain and swelling. Consistent with the mechanism of action of epcoritamab, tumour flare is likely due to the influx of T-cells into tumour sites following epcoritamab administration.

There are no specific risk factors for tumour flare that have been identified; however, there is a heightened risk of compromise and morbidity due to mass effect secondary to tumour flare in patients with bulky tumours located in close proximity to airways and/or a vital organ. Patients treated with epcoritamab should be monitored and evaluated for tumour flare at critical anatomical sites.

Patient card

The doctor must inform the patient of the risk of CRS and ICANS and any signs and symptoms of CRS and ICANS. Patients must be instructed to seek immediate medical attention if they experience signs and symptoms of CRS and/or ICANS. Patients should be provided with a patient card and instructed to carry the card at all times. This card describes symptoms of CRS and ICANS which, if experienced, should prompt the patient to seek immediate medical attention.

Immunisation

Live and/or live-attenuated vaccines should not be given during treatment with epcoritamab. Studies have not been conducted in patients who received live vaccines.

Excipients with known effect

This medicinal product contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially ‘sodium-free’.

This medicinal product contains 21.9 mg of sorbitol per vial.

This medicinal product contains 0.42 mg of polysorbate 80 per vial, equivalent to 0.4 mg/ml. Polysorbate 80 may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed. Transient elevation of certain proinflammatory cytokines by epcoritamab may suppress CYP450 enzyme activities. On initiation of epcoritamab therapy in patients being treated with CYP450 substrates with a narrow therapeutic index, therapeutic monitoring should be considered (see section 5.2).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in females

Women of childbearing potential should be advised to use effective contraception during treatment with epcoritamab and for at least 4 months after the last dose.

Pregnancy

Based on its mechanism of action, epcoritamab may cause foetal harm, including B-cell lymphocytopenia and alterations in normal immune responses, when administered to pregnant women. There are no data on the use of epcoritamab in pregnant women. Animal reproduction studies have not been conducted with epcoritamab. IgG1 antibodies, such as epcoritamab, can cross the placenta resulting in foetal exposure. Advise pregnant women of the potential risk to a foetus.

Epcoritamab is not recommended during pregnancy and in women of childbearing potential not using contraception.

Verify pregnancy status in females of reproductive potential prior to initiating epcoritamab treatment.

Breast-feeding

It is not known whether epcoritamab is excreted in human milk or its effect on milk production. Since IgGs are known to be present in milk, neonatal exposure to epcoritamab may occur via lactational transfer. Breast-feeding should be discontinued during treatment with epcoritamab and for at least 4 months after the last dose.

Fertility

No fertility studies have been conducted with epcoritamab (see section 5.3). The effect of epcoritamab on male and female fertility is unknown.

4.7 Effects on ability to drive and use machines

Epcoritamab has major influence on the ability to drive and use machines. Due to the potential for neurological events, such as ICANS, patients receiving epcoritamab are at risk of altered level of consciousness (see section 4.4). Patients who experience neurological signs and symptoms should be advised not to drive, cycle or use tools or potentially dangerous machines until symptoms resolve.

4.8 Undesirable effects

Summary of the safety profile

The safety of epcoritamab was evaluated in a non-randomised, single-arm GCT3013-01 study in 382 patients with relapsed or refractory large B-cell lymphoma (N=167), follicular lymphoma (N=129) and follicular lymphoma (3-step step-up dose schedule N=86) after two or more lines of systemic therapy and included all the patients who enrolled to the 48 mg dose and received at least one dose of epcoritamab.
The following adverse reactions have been reported with epcoritamab during clinical studies and post marketing experience.

The median duration of exposure to epcoritamab was 4.9 months (range: <1 to 30 months).

The most common adverse reactions (≥20%) were CRS (56%), injection site reactions (40%), fatigue (32%), viral infection (28%), neutropenia (28%), muscoskeletal pain (27%), pyrexia (22%), and diarrhoea (21%). The most common Grade 3-4 adverse reactions (≥2%) were neutropenia (23%), viral infections (9.2%), lymphopenia (8.9%), anaemia (7.1%), pneumonia (5.8%), thrombocytopenia (5.5%), fatigue (2.9%), febrile neutropenia (2.4%), and sepsis (2.4%).

Serious adverse reactions occurred in 50% of patients. The most common serious adverse reaction (≥10%) was CRS (34%). Fourteen patients (3.7%) experienced a fatal adverse reaction (pneumonia in 9 (2.4%) patients, viral infection in 4 (1.0%) patients, and ICANS in 1 (0.3%) patient).

Adverse reactions that led to discontinuation occurred in 6.8% of patients. Discontinuation of epcoritamab due to pneumonia occurred in 14 (3.7%) patients, viral infection in 8 (2.1%) patients, fatigue in 2 (0.5%) patients and CRS, ICANS, or diarrhoea occurred in 1 (0.3%) patient each.

Dose delays due to adverse reactions occurred in 42% of patients. Adverse reactions leading to dose delays (≥3% of patients) were viral infections (17%), CRS (11%), neutropenia (5.2%), pneumonia (4.7%), upper respiratory tract infection (4.2%) and pyrexia (3.7%).

Tabulated list of adverse reactions

Adverse reactions for epcoritamab from clinical studies (Table 7) are listed by MedDRA system organ class and are based on the following convention: 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); and very rare (< 1/10 000).

Table 7 Adverse reactions reported in patients with relapsed or refractory LBCL or FL treated with epcoritamab

System organ class / preferred term or adverse reaction	All grades	Grade 3-4
Infections and infestations		
Viral infection[a]	Very common	Common
Pneumonia[b]	Very common	Common
Upper respiratory tract infection[c]	Very common	Common

Fungal infection[d]	Common	
Sepsis[e]	Common	Common
Cellulitis	Common	Common
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Tumour flare	Common	
Blood and lymphatic system disorders		
Neutropenia[f]	Very common	Very common
Anaemia[g]	Very common	Common
Thrombocytopenia[h]	Very common	Common
Lymphopenia[i]	Very common	Common
Febrile neutropenia	Common	Common
Haemophagocytic lymphohistiocytosis[j]	Uncommon	Rare
Immune system disorders		
Cytokine release syndrome[j]	Very common	Common
Hypogammaglobulinaemia	Very common	Uncommon
Metabolism and nutrition disorders		
Decreased appetite	Very common	Uncommon
Hypokalaemia	Common	Common
Hypophosphatemia	Common	Common
Hypomagnesaemia	Common	Uncommon
Tumour lysis syndrome[k]	Common	Uncommon
Nervous system disorders		
Headache	Very common	Uncommon
Immune effector cell-associated neurotoxicity syndrome[j]	Common	
Cardiac disorders		
Cardiac arrhythmias[l]	Common	Uncommon
Respiratory, thoracic and mediastinal disorders		
Pleural effusion	Common	Common
Gastrointestinal disorders		
Diarrhoea	Very common	Uncommon
Abdominal Pain[m]	Very common	Common
Nausea	Very common	Uncommon
Vomiting	Common	Uncommon
Skin and subcutaneous tissue disorders		
Rash[n]	Very common	
Pruritus	Common	
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain[o]	Very common	Common
General disorders and administration site conditions		
Injection site reactions[p]	Very common	
Fatigue[q]	Very common	Common
Pyrexia[r]	Very common	Common
Oedema[s]	Very common	Common
Investigations		

Alanine aminotransferase increased	Common	Common
Aspartate aminotransferase increased	Common	Common
Blood creatinine increased	Common	
Blood sodium decreased[t]	Common	Uncommon
Alkaline phosphatase increased	Common	

Adverse reactions were graded using NCI CTCAE version 5.0
[a] Viral infection includes COVID-19, cytomegalovirus chorioretinitis, cytomegalovirus colitis, cytomegalovirus infection, cytomegalovirus infection reactivation, gastroenteritis viral, herpes simplex, herpes simplex reactivation, herpes virus infection, herpes zoster, oral herpes, post-acute COVID-19 syndrome, and varicella zoster virus infection
[b] Pneumonia includes COVID-19 pneumonia and pneumonia
[c] Upper respiratory tract infection includes laryngitis, pharyngitis, respiratory syncytial virus infection, rhinitis, rhinovirus infection, and upper respiratory tract infection
[d] Fungal infection includes candida infection, oesophageal candidiasis, oral candidiasis and oropharyngeal candidiasis
[e] Sepsis includes bacteraemia, sepsis, and septic shock
[f] Neutropenia includes neutropenia and neutrophil count decreased
[g] Anaemia includes anaemia and serum ferritin decreased
[h] Thrombocytopenia includes platelet count decreased and thrombocytopenia
[i] Lymphopenia includes lymphocyte count decreased and lymphopenia
[j] Events graded using American Society for Transplantation and Cellular Therapy (ASTCT) consensus criteria
[k] Clinical Tumour Lysis Syndrome was graded based on Cairo-Bishop
[l] Cardiac arrhythmias include bradycardia, sinus bradycardia, sinus tachycardia, supraventricular tachycardia, and tachycardia
[m] Abdominal pain includes abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, and abdominal tenderness
[n] Rash includes rash, rash erythematous, rash macular, rash maculo-papular, rash popular, rash pruritic, rash pustular and rash vesicular
[o] Musculoskeletal pain includes back pain, bone pain, flank pain, musculoskeletal chest pain, musculoskeletal pain, myalgia, neck pain, non-cardiac chest pain, pain, pain in extremity, and spinal pain
[p] Injection site reactions include injection site bruising, injection site erythema, injection site hypertrophy, injection site inflammation, injection site mass, injection site nodule, injection site oedema, injection site pain, injection site pruritus, injection site rash, injection site reaction, injection site swelling, and injection site urticaria
[q] Fatigue includes asthenia, fatigue, and lethargy
[r] Pyrexia includes body temperature increased and pyrexia
[s] Oedema includes face oedema, generalized oedema, oedema, oedema peripheral, peripheral swelling, swelling, and swelling face
[t] Blood sodium decreased includes blood sodium decreased and hyponatraemia

Description of selected adverse reactions

Cytokine release syndrome

2-step step-up dose schedule (large B-cell lymphoma and follicular lymphoma)
In study GCT3013-01, CRS of any grade occurred in 58% (171/296) of patients with large B-cell lymphoma and follicular lymphoma treated with epcoritamab at the 2-step step-up dose schedule. The incidence of Grade 1 was 35%, Grade 2 was 21%, and Grade 3 occurred in 2.4% of patients. Recurrent CRS occurred in 21% of patients

with CRS. CRS of any grade occurred in 9.8% of patients after the priming dose (Cycle 1 Day 1); 13% after the intermediate dose (Cycle 1 Day 8); 51% after the first full dose (Cycle 1 Day 15); 6.5% after the second full dose (Cycle 1 Day 22); and 3.7% after the third full dose (Cycle 2 Day 1) or beyond. The median time to onset of CRS from the most recent administered epcoritamab dose was 2 days (range: 1 to 12 days). The median time to onset after the first full dose was 19.3 hours (range: <0.1 days to 7 days). CRS resolved in 99% of events, and the median duration of CRS events was 2 days (range 1 to 54 days).

Dose delays due to CRS occurred in 9.1% of patients. Treatment was discontinued in 0.3% of patients due to CRS.

Of the 171 patients that experienced CRS, the most common signs and symptoms of CRS included pyrexia (99%), hypotension (32%) and hypoxia (16%). Other signs and symptoms of CRS in ≥3% of patients included chills (11%), tachycardia (including sinus tachycardia (11%)), headache (8.2%), nausea (4.7%), and vomiting (4.1%). Tocilizumab was used to manage the CRS event in 19% of patients, and corticosteroids were used in 12% of patients. Out of the 67 events treated with tocilizumab, 84% responded within four (4) days of treatment.

Hospitalizations due to CRS occurred in 34% of patients and the median time to CRS resolution in those who were hospitalized was 1 day (range <1 to 26 days).

3-step step-up dose schedule follicular lymphoma
In study GCT3013-01, CRS of any grade occurred in 49% (42/86) of patients treated with epcoritamab at the recommended follicular lymphoma 3-step step-up dose schedule. The incidence of Grade 1 was 40% and Grade 2 was 9%. There were no Grade ≥3 CRS events reported. Recurrent CRS occurred in 23% of patients. Most CRS events occurred during Cycle 1, where 48% of patients experienced an event. In Cycle 1, CRS occurred in 12% of patients after the priming dose (Cycle 1 Day 1), 5.9% of patients after the intermediate dose (Cycle 1 Day 8), 15% of patients after the second intermediate dose (Cycle 1 Day 15), and 37% of patients after the first full dose (Cycle 1 Day 22). The median time to onset of CRS from the most recent administered epcoritamab dose was 59 hours (range: 1 to 8 days). The median time to onset after the first full dose was 61 hours (range: 1 to 8 days). CRS resolved in 100% of patients and the median duration of CRS events was 2 days (range 1 to 14 days).

Serious adverse reactions due to CRS occurred in 28% of patients who received epcoritamab.
Dose delays due to CRS occurred in 19% of patients who received epcoritamab.

Of the 42 patients that experienced CRS at the recommended dose, the most common (≥10%) signs and symptoms of CRS included pyrexia (100%) and hypotension (14%). In addition to corticosteroid use, tocilizumab was used to manage CRS event in 12% of patients.

Immune effector cell associated neurotoxicity syndrome

In study GCT3013-01, ICANS occurred in 4.7% (18/382) of patients treated with epcoritamab; 3.1% experienced Grade 1 and 1.3% experienced Grade 2. One patient (0.3%) experienced an ICANS event of Grade 5 (fatal). The median time to first ICANS onset from the start of epcoritamab treatment (Cycle 1 Day 1) was 18 days (range: 8 to 141 days). ICANS resolved in 94% (17/18) of patients with supportive care. The median time to resolution of ICANS was 2 days (range: 1 to 9 days).

Dose delays due to ICANS occurred in 1.0% of patients. Treatment was discontinued in 0.3% of patients due to ICANS.

Serious infections

Large B-cell lymphoma
In study GCT3013-01, serious infections of any grade occurred in 25% (41/167) of patients with large B-cell lymphoma treated with epcoritamab. The most frequent serious infections were COVID-19 (6.6%), COVID-19 pneumonia (4.2%), pneumonia (3.6%), sepsis (2.4%), cellulitis (1.8%), upper respiratory tract infection (1.8%), bacteraemia (1.2%), septic shock (1.2%), and progressive multifocal leukoencephalopathy (1.2%). The median time to onset of first serious infection was 56 days (range: 4 to 631 days), with median duration of 15 days (range: 4 to 125 days). Grade 5 events (fatal serious) of infections occurred in 7 (4.2%) patients.

Dose delays due to serious infections occurred in 15% of patients. Treatment was discontinued in 6.0% of patients due to serious infections (see Section 4.4).

Follicular lymphoma
In study GCT3013-01, serious infections of any grade occurred in 32% (68/215) of patients with follicular lymphoma treated with epcoritamab. The most frequent serious infections included COVID-19 (8.8%), COVID-19 pneumonia (5.6%), pneumonia (3.7%), urinary tract infection (1.9%), and *Pneumocystis jirovecii* pneumonia (1.4%). The median time to onset of first serious infection from the start of epcoritamab treatment (Cycle 1 Day 1) was 81 days (range: 1 to 636 days), with median duration of 18 days (range: 4 to 249 days). Grade 5 events of infection occurred in 8 (3.7%) patients, 6 (2.8%) of which were attributed to COVID-19 or COVID-19 pneumonia.

Immunogenicity

Epcoritamab has the potential to induce anti-product antibodies (ADA). The incidence of antibodies to epcoritamab was low and all the patients with LBCL who were ADA positive had low titres (≥1 in 0.6% (1/158)) and all the patients with FL who were ADA positive had titers <1. Due to the low number of patients with ADAs, a meaningful analysis of the impact of ADAs on safety is limited (see section 5.2).

Neutropenia

In study GCT3013-01, neutropenia of any grade occurred in 28% (105/382) of patients, including 23% Grade 3-4 events. The median time to onset of first neutropenia/neutrophil count decreased event was 65 days (range: 2 to 750 days), with median duration of 15 days (range: 2 to 415 days). Of the 105 patients who had

neutropenia/neutrophil count decreased events, 61% received G-CSF to treat the events. Dose delays due to neutropenia occurred in 20 (5.2%) patients and there were no dose discontinuations due to neutropenia.

Tumour Lysis Syndrome
In study GCT3013-01, TLS occurred in 1.0% (4/382) of patients. Median time to onset was 18 days (range 8 to 33 days), and median duration was 3 days (range 2 to 4 days).

Tumour Flare
In study GCT3013-01, tumour flare occurred in 1.6% (6/382) of patients, all of which were grade 2. The median time to onset was 19.5 days (range 9 to 34 days), and median duration was 9 days (range 1 to 50 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 Yellow Card Scheme: Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

In the event of overdose, monitor the patient for any signs or symptoms of adverse reactions and administer appropriate supportive treatment.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, other monoclonal antibodies and antibody drug conjugates, ATC code: L01FX27

Mechanism of action

Epcoritamab is a humanised IgG1-bispecific antibody that binds to a specific extracellular epitope of CD20 on B cells and to CD3 on T cells. CD20 is expressed on most human B-cell lymphomas and leukaemias and on B cells in peripheral blood, but not hematopoietic stem cells or plasma cells. The activity of epcoritamab is dependent upon simultaneous engagement of CD20-expressing cancer cells and CD3-expressing endogenous T cells by epcoritamab that induces specific T-cell activation and T-cell-mediated killing of CD20-expressing cells, as epcoritamab does not have direct immune effector mechanisms.

Epcoritamab Fc region is silenced for direct immune effector mechanisms, such as antibody-dependent cellular cytotoxicity (ADCC), complement-dependent cellular cytotoxicity (CDC), and antibody-dependent cellular phagocytosis (ADCP).

Pharmacodynamic effects

Epcoritamab induced depletion of circulating B-cells (defined as CD19 B-cell counts ≤10 cell/µl) in subjects who have detectable B cells at treatment initiation after the first full dose (48 mg) which was sustained while patients remained on treatment. Subsequent treatment with epcoritamab induced expansion and activation of circulating T-cells from baseline.

In study GCT3013-01, following subcutaneous administration of epcoritamab at the recommended 2-step step-up dose schedule in patients with LBCL, transient and modest elevations of circulating levels of selected cytokines (IFN-γ, TNFα, IL-6, IL-2, and IL-10) occurred, mostly after the first full dose (48 mg) with peak levels between 1 to 4 days. Levels returned to baseline prior to the subsequent full dose.

In study GCT3013-01, following subcutaneous administration of epcoritamab at the recommended 3-step step-up dose schedule in patients with FL, median IL-6 levels associated with CRS risk remained consistently low after each dose in Cycle 1 and beyond, particularly after the first full dose, compared to patients who received the 2-step step-up dose.

Clinical efficacy and safety

Diffuse large B-cell lymphoma
Study EPCORE NHL-1 (GCT3013-01) was an open-label, multi-cohort, multicentre, single-arm trial that evaluated epcoritamab as monotherapy in patients with relapsed or refractory large B-cell lymphoma (LBCL) after two or more lines of systemic therapy. The study included patients with CD20 positive LBCL based on any representative pathology report, patients who had failed prior autologous hematopoietic stem cell transplantation (HSCT) or were ineligible for autologous HSCT, patients who had lymphocyte counts $<5\times10^9$/L, and patients with at least 1 prior anti-CD20 monoclonal antibody-containing therapy. The study excluded patients with CNS (central nervous system) involvement of lymphoma**,** seizure disorder requiring therapy, allogeneic HSCT or solid organ transplant, chronic ongoing infectious diseases, any patients with known impaired T-cell immunity, a creatinine clearance of less than 45 ml/min, alanine aminotransferase >3 times the upper limit of normal and clinically significant cardiac disease, including cardiac ejection fraction less than 45%.

Efficacy was evaluated in 139 patients with DLBCL within Study EPCORE NHL-1. Patients received epcoritamab subcutaneously (SC) in cycles of 4 weeks, i.e., 28 days. Epcoritamab was administered at the recommended 2-step step-up dose schedule as a monotherapy as follows:

- Cycle 1: epcoritamab 0.16 mg on Day 1, 0.8 mg on Day 8, 48 mg on Day 15 and Day 22
- Cycles 2-3: epcoritamab 48 mg on Days 1, 8, 15, and 22
- Cycles 4-9: epcoritamab 48 mg on Days 1 and 15
- Cycles 10 and beyond: epcoritamab 48 mg on Day 1

Patients continued to receive epcoritamab until disease progression or unacceptable toxicity.

The demographics and baseline characteristics are shown in Table 8.

Table 8 - Demographics and baseline characteristics of patients with DLBCL in EPCORE NHL-1 study

Characteristics	**(N=139)**
Age	
Median, years (min, max)	66 (22, 83)
Males, n (%)	85 (61)
Race n, %	
White,	84 (60)
Black, or African American	0
Asian	27 (19)
Other	5 (4)
Not Reported	23 (17)
ECOG performance status; %	
0	67 (48)
1	67 (48)
2	5 (4)
Number of prior lines of anti-lymphoma therapy, %	
Median (min, max)	3 (2, 11)
2	41 (30)
3	47 (34)
≥4	51 (37)
DLBCL Disease history; %	
De Novo DLBCL	97 (70)
DLBCL transformed from indolent lymphoma	40 (29)
FISH Analysis Per Central lab, N=88	
Double-hit/Triple-hit lymphoma, (%)	12 (14)
Prior therapy; (%)	
Prior CAR-T	53 (38)
Prior autologous HSCT	26 (19)
Primary refractory disease[a]	82 (59)
Refractory to ≥2 consecutive lines of prior anti-lymphoma therapy[b]	104 (75)
Refractory to the last line of systemic antineoplastic therapy[b]	114 (82)
Refractory to prior anti-CD20 therapy	117 (84)
Refractory to CAR-T	39 (28)

[a]A patient is considered to be primary refractory if they are refractory to frontline anti-lymphoma therapy.
[b]A patient is considered to be refractory if they experience disease progression or stable disease as best response or disease progression within 6 months after therapy completion.

Efficacy was established based on overall response rate (ORR) determined by Lugano criteria (2014) as assessed by Independent Review Committee (IRC). The median follow-up time was 15.7 months (range: 0.3 to 23.5 months).

In this study, 7.9% (11/139) of patients had initial progressive disease (PD) by Lugano or indeterminate response (IR) by LYRIC and later obtained a partial response (PR) or complete response (CR).

Table 9 - Efficacy results in study EPCORE NHL-1 in patients with DLBCL

Endpoint IRC assessment	Epcoritamab (N=139)
ORR[a], n (%)	86 (62)
(95% CI)	(53.3, 70)
CR, n (%)	54 (39)
(95% CI)	(30.7, 47.5)
PR	32 (23)
(95% CI)	(16.3, 30.9)
DOR[b]	
Median (95% CI), months	15.6 (9.7, NR)
DOCR[b]	
Median (95% CI), months	NR (14.3, NR)
TTR, median (range), months	1.4 (1.0, 8.4)
CI = confidence interval; CR = complete response; DOR = duration of response; IRC = independent review committee; ORR = overall response rate; PR = partial response; TTR = time to response [a] ORR=CR+PR; Determined by Lugano criteria (2014) as assessed by independent review committee (IRC) [b] Included patients with initial PD by Lugano or IR by LYRIC (pseudo-progression) who later obtained PR/CR.	

The median time to CR was 2.6 months (range: 1.2 to 10.2 months).

Median DOR (CR and PR) in patients who achieved a CR was 17.3 months (95% CI:15.6, NR) compared to a median DOR of 2.1 months (95% CI; 1.4, 3.1) in those who achieved a partial response.

Response durations were longer in patients who achieved CR, as compared to patients with a best response of partial response (PR).

Follicular lymphoma

Study GCT3013-01 was an open-label, multi-cohort, multicentre, single-arm trial that evaluated epcoritamab as monotherapy in patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy. The study includes a dose escalation part, an expansion part and a 3-step step-up dose optimisation part. The expansion part of the study included an aggressive non-Hodgkin lymphoma (aNHL) cohort, an indolent NHL (iNHL) cohort and a mantle-cell lymphoma (MCL) cohort. The pivotal iNHL cohort, included patients with FL. Patients included in the study were required to have documented CD20+ mature B-cell neoplasm according to WHO classification 2016 or WHO classification 2008 based on representative pathology report with histologic confirmed FL 1-3A at initial diagnosis without clinical or pathological evidence of transformation. All patients had relapsed or refractory disease to the last prior line therapy and previously treated with at least 2 lines of systemic antineoplastic therapy, including at least 1 anti-CD20 monoclonal antibody-containing therapy and an alkylating agent or lenalidomide. The study excluded patients with CNS involvement of lymphoma**,** allogeneic HSCT or solid organ transplant, ongoing active infectious diseases, any patients with known impaired T-cell immunity, a creatinine clearance of less than 45 ml/min, alanine aminotransferase >3 times the upper limit of normal and cardiac ejection fraction less than 45%. Efficacy was evaluated in 128 patients

who had received epcoritamab subcutaneously (SC) in cycles of 4 weeks, i.e., 28 days. Epcoritamab was administered as a monotherapy in a 2-step step-up dose schedule as follows:

- Cycle 1: epcoritamab 0.16 mg on Day 1, 0.8 mg on Day 8, 48 mg on Day 15 and 48 mg on Day 22
- Cycles 2-3: epcoritamab 48 mg on Days 1, 8, 15, and 22
- Cycles 4-9: epcoritamab 48 mg on Days 1 and 15
- Cycles 10 and beyond: epcoritamab 48 mg on Day 1

Patients continued to receive epcoritamab until disease progression or unacceptable toxicity.

The median number of cycles initiated was 8 and 60% received 6 cycles.

The demographics and baseline characteristics are shown in Table 10.

Table 10 - Demographics and baseline characteristics of patients with FL in GCT3013-01 study

Characteristics	**(N = 128)**
Age	
Median, years (min, max)	65 (39, 84)
< 65 years, n (%)	61 (48)
65 to < 75 years, n (%)	50 (39)
≥ 75 years, n (%)	17 (13)
Males, (%)	79 (62)
Race, n (%)	
White	77 (60)
Asian	7 (6)
Other	2 (1.6)
Not Reported	42 (33)
ECOG performance status; n (%)	
0	70 (55)
1	51 (40)
2	7 (6)
Number of prior lines of therapies, n (%)	
Median (min, max)	3 (2, 9)
2	47 (37)
3	41 (32)
≥4	40 (31)
Ann Arbor Staging; (%)	
Stage III/IV	109 (85)
FLIPI at baseline, n (%)	
2	31 (24)
3- 5	78 (61)
Bulky Disease, n (%)	33 (26)

Characteristics	**(N = 128)**
Prior Therapy; n (%)	
Autologous stem cell transplant	24 (19)
Chimeric antigen receptor (CAR)-T cell therapy	6 (5)
Rituximab plus lenalidomide therapy	27 (21)
PI3K inhibitor	29 (23)
Progression of disease within 24 months of first systemic therapy	67 (52)
Refractory to:	
≥ 2 consecutive lines of prior anti-lymphoma therapy	70 (55)
The last line of systemic antineoplastic therapy	88 (69)
Prior anti-CD20 monoclonal antibody therapy	101 (79)
Both anti-CD20 monoclonal antibody and alkylator therapy	90 (70)

Efficacy was established based on overall response rate (ORR) determined by Lugano criteria (2014) as assessed by Independent Review Committee (IRC). The median follow-up for DOR was 16.2 months. Efficacy results are summarised in Table 11.

Table 11 - Efficacy Results in Study GCT3013-01 in FL Patients

Endpoint [a] **IRC assessment**	**Epcoritamab (N=128)**
ORR [b], n (%)	106 (83)
(95% CI)	(75.1, 88.9)
CR[b], n (%)	81 (63)
(95% CI)	(54.3, 71.6)
PR [b], n (%)	25 (20)
(95% CI)	(13.1, 27.5)
DOR[b]	
Median (95% CI), months	21.4 (13.7, NR)
DOCR[b]	
Median (95% CI), months	NR (21.4, NR)
12-month estimate, % (95% CI)	78.6 (67.3, 86.4)
TTR, median (range), months	1.4 (1, 3)

CI = confidence interval; CR = complete response; DOR = duration of response; DOCR = duration of complete response; IRC = independent review committee; ORR = overall response rate; PFS = progression-free survival; TTR = time to response

[a] determined by Lugano criteria (2014) as assessed by independent review committee (IRC)

[b] Included patients with initial PD by Lugano or IR by LYRIC who later obtained PR/CR.

The median time to CR was 1.5 months (range: 1.2 to 11.1 months).

Immunogenicity

The incidence of treatment-emergent ADAs with the 2-step step-up dose schedule (0.16/0.8/48 mg) in the combined population of DLBCL and FL was 3.4% (3.4 % positive, 93.9% negative and 2.7% indeterminate, N=261 evaluable patients) and 3.3% (3.3% positive, 95% negative and 1.7% indeterminate, N= 60 evaluable patients), in studies GCT3013-01 and GCT3013-04, respectively.
The incidence of treatment-emergent ADAs with the 3-step step-up dose schedule (0.16/0.8/3/48 mg) in the FL optimisation cohort was 7% (7% positive, 91.5% negative and 1.4% indeterminate, N=71 evaluable patients) in study GCT3013-01. A subject is classified as indeterminate if the patient is confirmed ADA positive at baseline but there is no confirmed positive on-treatment record or if confirmed ADA positive on treatment record titre are equal or lower than baseline.

Paediatric population

The Medicines and Healthcare products Regulatory Agency has deferred the obligation to submit the results of studies with epcoritamab in one or more subsets of the paediatric population in the treatment of mature B-cell malignancies, as per paediatric investigation plan (PIP) decision, for the granted indication (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 Medicines and Healthcare products Regulatory 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

The population pharmacokinetics following subcutaneous administration of epcoritamab was described by a two-compartment model with first order subcutaneous absorption and target-mediated drug elimination. The moderate to high pharmacokinetic variability for epcoritamab was observed and characterised by inter-individual variability (IIV) ranging from 25.7% to 137.5% coefficient of variation (CV) for epcoritamab PK parameters.

In patients with LBCL in study GCT3013-01, based on individually estimated exposures using population pharmacokinetic modelling, following the recommended 2-step step-up dose schedule SC dose of epcoritamab 48 mg, the geometric mean (% CV) C_{max} of epcoritamab is 10.8 mcg/ml (41.7%) and AUC0-7d is 68.9 day*mcg/ml (45.1%) at the end of the weekly dosing schedule.

The geometric mean (% CV) C_{max} of epcoritamab is 7.52 mcg/ml (41.1%) and AUC0-14d is 82.6 day*mcg/ml (49.3%) at the end of q2w schedule.

The geometric mean (% CV) C_{max} of epcoritamab is 4.76 mcg/ml (51.6%) and AUC0-28d is 74.3 day*mcg/ml (69.5%) at steady state during the q4w schedule.

Exposure parameters of epcoritamab in patients with FL were consistent with the exposure parameters seen in the patients with LBCL. Epcoritamab exposures are similar between FL subjects who received the 3-step step-up dose schedule and 2-step step-up dose schedule except for transiently lower trough concentrations, as expected,

at Cycle 1 Day 15 after the second intermediate dose (3 mg) with 3-step step-up dose schedule compared first full 48 mg dose with 2-step step-up dose schedule.

Absorption

The peak concentrations occurred around 3-4 days (T_{max}) in patients with LBCL receiving the 48 mg full dose.

Distribution

The geometric mean (% CV) central volume of distribution is 8.27 l (27.5%) based on population PK modelling.

Biotransformation

The metabolic pathway of epcoritamab has not been directly studied. Like other protein therapeutics, epcoritamab is expected to be degraded into small peptides and amino acids via catabolic pathways.

Elimination

Epcoritamab is expected to undergo saturable target mediated clearance. The geometric mean (% CV) clearance (l/day) is 0.441 (27.8%). The half-life of epcoritamab is concentration dependent. The population PK model-derived geometric mean half-life of full dose epcoritamab (48 mg) ranged from 22 to 25 days based on frequency of dosing.

Special populations

No clinically important effects on the pharmacokinetics of epcoritamab were observed based on age (20 to 89 years), sex, or race/ethnicity (white, Asian, and other), mild to moderate renal impairment (CLcr ≥ 30 ml/min to CLcr < 90 ml/min), and mild hepatic impairment (total bilirubin ≤ ULN and AST > ULN, or total bilirubin 1 to 1.5 times ULN and any AST) after accounting for differences in bodyweight. No patients with severe to end-stage renal disease (CLcr <30 ml/min) or severe hepatic impairment (total bilirubin > 3 times ULN and any AST) have been studied. There is very limited data in moderate hepatic impairment (total bilirubin >1.5 to 3 times ULN and any AST, N=1). Therefore, the pharmacokinetics of epcoritamab is unknown in these populations.

In patients who received the recommended dosage of epcoritamab, Cycle 1 median average concentration was 13% lower in the higher body weight (BW) group (85 to 144 kg) and 37% higher in the lower BW group (39 to 65 kg) compared to patients with BW of 65 to less than 85 kg.

Paediatric

The pharmacokinetics of epcoritamab in paediatric patients has not been established.

5.3 Preclinical safety data

Carcinogenicity

Carcinogenicity studies have not been conducted with epcoritamab.

Mutagenicity

Mutagenicity studies have not been conducted with epcoritamab**.**

Impairment of fertility

Animal fertility studies have not been conducted with epcoritamab, however, epcoritamab did not cause toxicological changes in the reproductive organs of male or female cynomolgus monkeys at doses up to 1 mg/kg/week in intravenous general toxicity study of 5-week duration.

Animal pharmacology and/or toxicology

Effects generally consistent with the pharmacologic mechanism of action of epcoritamab were observed in cynomolgus monkeys. These findings included dose-related adverse clinical signs (including vomiting, decreased activity, and mortality at high doses) and cytokine release, reversible hematologic alterations, reversible B-cell depletion in peripheral blood, and reversible decreased lymphoid cellularity in secondary lymphoid tissues.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium acetate trihydrate

Acetic acid

Sorbitol (E420)

Polysorbate 80

Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products and/or diluents except those listed in section 6.6.

6.3 Shelf life

Unopened vial

2 years

Diluted or prepared epcoritamab

Chemical and physical in-use stability has been demonstrated for 24 hours at 2 °C to 8 °C including up to 12 hours at room temperature (20-25 °C).

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

Minimise exposure to daylight. Allow epcoritamab solution to equilibrate to room temperature before administration. Discard unused epcoritamab solution beyond the allowable storage time.

6.4 Special precautions for storage

Store and transport refrigerated (2°C to 8°C).
Keep the vial in the outer carton in order to protect from light.
Do not freeze. Do not shake.

For storage conditions after dilution/first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Type I glass vial with a bromobutyl rubber stopper coated with fluoropolymer at the contact site and an aluminium seal with a plastic light blue flip off cap, containing 4 mg per 0.8 ml solution for injection.

Each carton contains one vial.

6.6 Special precautions for disposal

Preparation of epcoritamab
This entire section must be read carefully before preparation of epcoritamab. **Certain doses** (the priming (0.16 mg) and intermediate dose (0.8 mg)) of epcoritamab require **dilution** prior to administration. Epcoritamab can be diluted using two different methods which are either the vial method or the syringe method.

All instructions provided below must be followed as improper preparation may lead to improper dose.

Epcoritamab must be prepared and administered by a healthcare provider as a subcutaneous injection.
Each vial of epcoritamab is intended for single use only.

Each vial contains an overfill that allows withdrawal of the labelled amount.

The administration of epcoritamab takes place over the course of 28-day cycles, following the dosing schedule in Section 4.2.

Epcoritamab should be inspected visually for particulate matter and discolouration prior to administration. The solution for injection should be a colourless to slightly yellow solution. Do not use if the solution is discoloured, or cloudy, or if particles are present.

Epcoritamab has to be prepared using aseptic technique.
Filtration of the diluted solution is not required. However, if the diluted solution is filtered, do not use filters made of nylon.

Table 12 outlines the materials needed for preparation of the 0.16 mg and 0.8 mg doses of epcoritamab using sterile vials.

Table 12 - Materials needed to prepare epcoritamab 0.16 mg dose and epcoritamab 0.8 mg dose

Materials needed to prepare epcoritamab 0.16 mg dose and epcoritamab 0.8 mg dose	
Priming dose (0.16 mg)	**Intermediate dose (0.8 mg)**
4 mg/0.8 ml epcoritamab vial with **light blue** cap	4 mg/0.8 ml epcoritamab vial with **light blue** cap
0.9% sodium chloride injection	0.9% sodium chloride injection
Two empty sterile vials (10 or 20 ml vial size)	One empty sterile vial (10 or 20 ml vial size)
Recommended syringe sizes	Recommended syringe sizes
• Two 1 ml syringes • One 3 ml syringe • One 5 ml syringe • One 10 ml syringe	• Two 1 ml syringes • One 5 ml syringe

Preparation of diluted epcoritamab using the empty sterile vial method
0.16 mg priming dose preparation instructions - ***(2 dilutions required)*** **– empty sterile vial method**

Use an appropriately sized syringe, vial and needle for each transfer step.

1) Prepare the epcoritamab vial
   a) Retrieve one 4 mg/0.8 ml epcoritamab vial with a **light blue** cap from the refrigerator.

b) Allow the vial to come to room temperature for no more than 1 hour.
c) Gently swirl the epcoritamab vial.

DO NOT invert, vortex or vigorously shake the vial.

2) Perform the first dilution
   a) Label an appropriately sized empty vial as **"dilution A"**.
   b) Transfer **0.8 ml of epcoritamab** into the **dilution A** vial.
   c) Transfer **4.2 ml of sodium chloride 9 mg/ml (0.9%) sterile solution** into the **dilution A** vial. The initial diluted solution contains 0.8 mg/mL of epcoritamab.
   d) Gently swirl the **dilution A** vial for 30 – 45 seconds.

3) Perform the second dilution
   a) Label an approximately sized empty vial as **"dilution B"**.
   b) Transfer **2.0 ml of solution** from the **dilution A** vial into the **dilution B** vial. The **dilution A** vial is no longer needed and should be discarded.
   c) Transfer **8.0 ml of sodium chloride 9 mg/ml (0.9%) sterile solution** into the **dilution B** vial to make a final concentration of 0.16 mg/ml.
   d) Gently swirl the **dilution B** vial for 30 – 45 seconds.

4) Withdraw the dose
   Withdraw **1.0 ml of the diluted epcoritamab** from the **dilution B** vial into a syringe.
   The **dilution B** vial is no longer needed and should be discarded.

5) Label the syringe
   Label the syringe with product name, the dose strength (0.16 mg), date and the time of day.
   For storage of the diluted epcoritamab, see section 6.3.

6) Discard the vial containing unused epcoritamab in accordance with local requirements.

<u>0.8 mg intermediate dose preparation instructions - ***(1 dilution required)*** **– empty sterile vial method**</u>

Use an appropriately sized syringe, vial and needle for each transfer step.

1) Prepare the epcoritamab vial
   a) Retrieve one 4 mg/0.8 ml epcoritamab vial with a **light blue** cap from the refrigerator.
   b) Allow the vial to come to room temperature for no more than 1 hour.
   c) Gently swirl the epcoritamab vial.

DO NOT invert, vortex or vigorously shake the vial.

2) Perform the dilution
   a) Label an appropriately sized empty vial as "**dilution A**".
   b) Transfer **0.8 ml of epcoritamab** into the **dilution A** vial.
   c) Transfer **4.2 ml of sodium chloride 9 mg/ml (0.9%) sterile solution** into the **dilution A** vial to make a final concentration of 0.8 mg/ml.
   d) Gently swirl the **dilution A** vial for 30 to 45 seconds.

3) Withdraw the dose

Withdraw **1.0 ml of the diluted epcoritamab** from the **dilution A** vial into a syringe.

The **dilution A** vial is no longer needed and should be discarded.

4) Label the syringe

Label the syringe with the product name, dose strength (0.8 mg), date and the time of day.

For storage of the diluted epcoritamab, see section 6.3.

5) Discard the vial containing unused epcoritamab in accordance with local requirements.

Preparation of diluted epcoritamab using the sterile syringe method

<u>0.16 mg priming dose preparation instructions - **2 dilutions required – sterile syringe method**</u>

Use an appropriately sized syringe and needle for each transfer step.

1) Prepare epcoritamab vial
   a. Retrieve one 4 mg/0.8 ml epcoritamab vial with the **light blue** cap from the refrigerator.
   b. Allow the vial to come to room temperature for no more than 1 hour.
   c. Gently swirl the epcoritamab vial.

DO NOT vortex or vigorously shake the vial.

2) Perform first dilution
   a. Label an appropriately sized syringe as **"dilution A"**.
   b. Withdraw **4.2 ml of sodium chloride 9 mg/ml (0.9%) sterile solution** into the **dilution A** syringe. Include approximately 0.2 ml air in the syringe.
   c. In a new syringe labelled as **"syringe 1"**, withdraw **0.8 ml of epcoritamab.**
   d. Connect the two syringes and push the **0.8 ml of epcoritamab** into the **dilution A** syringe. The initially diluted solution contains 0.8 mg/ml of epcoritamab.
   e. Gently mix by inverting the connected syringes 180 degrees 5 times.
   f. Disconnect the syringes and discard **syringe 1**.

3) Perform second dilution
   a. Label an appropriately sized syringe as **"dilution B"**.
   b. Withdraw **8 ml of sodium chloride 9 mg/ml (0.9%) sterile solution** into the **dilution B** syringe. Include approximately 0.2 ml air in the syringe.
   c. Label another appropriately sized syringe as **"syringe 2"**.
   d. Connect **syringe 2** to the **dilution A** syringe and transfer **2 ml of solution** into **syringe 2**. The **dilution A** syringe is no longer needed and should be discarded.

e. Connect **syringe 2** to the **dilution B** syringe and push the **2 ml of solution** into the **dilution B** syringe to make a final concentration of 0.16 mg/ml. f. Gently mix by inverting the connected syringes 180 degrees 5 times. g. Disconnect the syringes and discard **syringe 2**.
4) Withdraw dose Connect and transfer **1 ml of the diluted epcoritamab** from the **dilution B** syringe into a new syringe. The **dilution B** syringe is no longer needed and should be discarded.
5) Label syringe Label the syringe with the product name, dose strength (0.16 mg), date and the time of day.
6) Discard the vial and any unused portion of epcoritamab in accordance with local requirements.

<u>0.8 mg intermediate dose preparation instructions - **1 dilution required – sterile syringe method**</u>

Use an appropriately sized syringe and needle for each transfer step.

1) Prepare epcoritamab vial a. Retrieve one 4 mg/0.8 ml epcoritamab vial with the **light blue** cap from the refrigerator. b. Allow the vial to come to room temperature for no more than 1 hour. c. Gently swirl the epcoritamab vial. **DO NOT** vortex or vigorously shake the vial.
2) Perform dilution a. Label an appropriately sized syringe as **"dilution A"**. b. Withdraw **4.2 ml of sodium chloride 9 mg/ml (0.9%) sterile solution** into the **dilution A** syringe. Include approximately 0.2 ml air in the syringe. c. In a new syringe labelled as "**syringe 1**", withdraw **0.8 ml of epcoritamab.** d. Connect the two syringes and push the **0.8 ml of epcoritamab** into the **dilution A** syringe to make a final concentration of 0.8 mg/ml. e. Gently mix by inverting the connected syringes 180 degrees 5 times. f. Disconnect the syringes and discard **syringe 1**.
3) Withdraw dose Connect a new syringe to the **dilution A** syringe and transfer **1 ml of the diluted epcoritamab** into the new syringe. The **dilution A** syringe is no longer needed and should be discarded.
4) Label syringe Label the syringe with the product name, dose strength (0.8 mg), date and the time of day.
5) Discard the vial and any unused portion of epcoritamab in accordance with local

requirements.

3 mg second intermediate dose preparation instructions- **No dilution required**
Epcoritamab 3 mg dose is required for FL patients only (see Section 4.2).

1) Prepare epcoritamab vial a) Retrieve one 4 mg/0.8 ml epcoritamab vial with the **light blue** cap from the refrigerator. b) Allow the vial to come to room temperature for no more than 1 hour. c) Gently swirl the epcoritamab vial. **DO NOT** vortex, or vigorously shake the vial.
2) Withdraw dose Withdraw **0.6 ml of epcoritamab** into a syringe.
3) Label syringe Label the syringe with the product name, dose strength (3 mg), date and the time of day. For storage of the prepared epcoritamab, see section 6.3.
4) Discard the vial and any unused portion of epcoritamab in accordance with local requirements.

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

7 MARKETING AUTHORISATION HOLDER

AbbVie Ltd
Maidenhead
SL6 4UB
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 41042/0092

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

19/08/2025

10 DATE OF REVISION OF THE TEXT

09/02/2026