Tepkinly® 4 mg/0.8 ml
Tepkinly® 48 mg

1. NAME OF THE MEDICINAL PRODUCT

Tepkinly 4 mg/0.8 ml
Tepkinly 48 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Tepkinly 4 mg/0.8 ml, solution for injection
Epcoritamab 5 mg/ml.
Each 0.8 ml vial contains 4 mg of epcoritamab.

Tepkinly 48 mg, solution for injection
Epcoritamab 60 mg/ml.
Each 0.8 ml vial contains 48 mg of epcoritamab.

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

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 28.8 mg of sorbitol and 0.42 mg of 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 osmolality of approximately 211 mOsm/kg.

4. CLINICAL PARTICULARS

Patient safety information Card
The marketing of Tepkinly is subject to a risk management plan (RMP) including a 'Patient safety information card'. The 'Patient safety information card', emphasizes important safety information that the patient should be aware of before and during treatment. Please explain to the patient the need to review the card before starting treatment.

4.1 Therapeutic indications

Tepkinly is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), not otherwise specified, including DLBCL arising from indolent lymphoma, and high-grade B cell lymphoma after two or more lines of systemic therapy.

Tepkinly in combination with lenalidomide and rituximab is indicated for the treatment of adult patients with relapsed or refractory follicular lymphoma (FL).

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 therapy. At least 1 dose of tocilizumab for use in the event of CRS should be available prior to epcoritamab 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

Recommended pre-medication and dose schedule

Tepkinly as monotherapy

Tepkinly should be administered according to the following step-up dose schedule in 28-day cycles which is outlined in Table 1 for patients with diffuse large B-cell lymphoma and Table 2 for patients with follicular lymphoma.

Table 1 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 2 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.

Tepkinly in combination with lenalidomide and rituximab

Administer Tepkinly in 28-day cycles for a total of 12 cycles or until disease progression or unacceptable toxicity, whichever occurs first.

Table 3: Tepkinly 3-step step-up dose schedule in combination with lenalidomide and rituximab for patients with follicular lymphoma

Indication	Cycle	Day	Dose of TEPKINLY	
Follicular Lymphoma	Cycle 1	1	Step-up dose 1	0.16 mg
		8	Step-up dose 2	0.8 mg
		15	Step-up dose 3	3 mg
		22	First full dose	48 mg
	Cycles 2 and 3	1, 8, 15, and 22	48 mg	
	Cycles 4 to 12	1	48 mg	

Administer Tepkinly in combination with lenalidomide 20 mg (Days 1 to 21 in Cycles 1 to 12) and rituximab 375 mg/m^2 (Cycles 1 to 5). Refer to the lenalidomide prescribing information and rituximab prescribing information for the respective dosage recommendations, including lenalidomide dosage recommendations for patients with renal insufficiency.

Premedications and prophylaxis

Details on recommended pre-medication for cytokine release syndrome (CRS) are shown in Table 4.

Table 4 Epcoritamab pre-medication

Cycle	Patient requiring pre-medication	Pre-medication	Administration
Cycle 1	All patients	Dexamethasone[b] (15 mg oral or intravenous) or Prednisolone (100 mg oral or intravenous) or equivalent	• 30-120 minutes prior to each weekly administration of epcoritamab • And for three consecutive days following each

			weekly administration of epcoritamab in Cycle 1
		• Diphenhydramine (50 mg oral or intravenous) or equivalent • Paracetamol (650 to 1,000 mg oral)	• 30-120 minutes prior to each weekly administration of epcoritamab
Cycle 2 and beyond	Patients who experienced Grade 2 or 3[a] CRS with previous dose	Dexamethasone[b] (15 mg oral or intravenous) or Prednisolone (100 mg oral or intravenous) or equivalent	• 30-120 minutes prior to next administration of epcoritamab after a grade 2 or 3[a] CRS event • And for three consecutive days following the next administration of epcoritamab until epcoritamab is given without subsequent any grade of CRS
[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			

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

Thromboprophylaxis
Refer to the lenalidomide prescribing information for recommendations on prophylaxis for venous and arterial thrombotic events.

Tepkinly should be administered to adequately hydrated patients.

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.

Patients should be monitored for signs and symptoms of CRS and/or immune effector cell-associated neurotoxicity syndrome (ICANS) and managed per current practice guidelines following epcoritamab administration. Patients should be counselled on the signs and symptoms associated with CRS and

ICANS and on seeking immediate medical attention should signs or symptoms occur at any time (see section 4.4).

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 and/or ICANS.

For patients with FL assess whether hospitalization or outpatient monitoring is appropriate based on comorbidities or other situational factors for the Cycle 1 Day 22 dosage of 48 mg.

Dose 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 5. Patients who experience CRS should be monitored more frequently during next scheduled epcoritamab administration.

Table 5 CRS grading and management guidance

Grade[a]	Recommended therapy	Epcoritamab dose modification
Grade 1 • Fever (temperature ≥ 38 °C)	Provide supportive care such as antipyretics and intravenous hydration Dexamethasone[b] may be initiated In cases of advanced age, high tumour burden, circulating tumour cells, fever refractory to antipyretics • Anti-cytokine therapy, tocilizumab[d], should be considered For CRS with concurrent ICANS refer to **Table 6**	Hold epcoritamab until resolution of CRS event
Grade 2 • Fever (temperature ≥ 38 °C) and • Hypotension not requiring vasopressors and/or • Hypoxia requiring low-flow oxygen[e] by nasal cannula or blow-by	Provide supportive care such as antipyretics and intravenous hydration Dexamethasone[b] should be considered Anti-cytokine therapy, tocilizumab[d], is recommended If CRS is refractory to dexamethasone and tocilizumab: • Alternative immunosuppressants[g] and methylprednisolone 1,000 mg/day intravenously should be administered until clinical improvement For CRS with concurrent ICANS refer to **Table 6**	Hold epcoritamab until resolution of CRS event
Grade 3 • Fever (temperature ≥ 38 °C) and • Hypotension requiring a vasopressor with or without vasopressin and/or	Provide supportive care such as antipyretics and intravenous hydration Dexamethasone[c] should be administered Anti-cytokine therapy, tocilizumab[d], is recommended If CRS is refractory to dexamethasone and tocilizumab:	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

Grade[a]	Recommended therapy	Epcoritamab dose modification
• Hypoxia requiring high-flow oxygen[f] by nasal cannula, facemask, non-rebreather mask, or venturi mask	• Alternative immunosuppressants[g] and methylprednisolone 1,000 mg/day intravenously should be administered until clinical improvement For CRS with concurrent ICANS refer to **Table 6**	72 hours, epcoritamab should be discontinued
Grade 4 • Fever (temperature ≥ 38 °C) and • 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 Dexamethasone[c] should be administered Anti-cytokine therapy, tocilizumab[d], is recommended If CRS is refractory to dexamethasone and tocilizumab: • Alternative immunosuppressants[g] and methylprednisolone 1,000 mg/day intravenously should be administered until clinical improvement For CRS with concurrent ICANS refer to **Table 6**	Permanently discontinue epcoritamab

[a]CRS graded according to ASTCT consensus criteria
[b]Dexamethasone should be administered at 10-20 mg per day (or equivalent)
[c]Dexamethasone should be administered at 10-20 mg intravenously every 6 hours
[d]Tocilizumab 8 mg/kg intravenously 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
[e]Low-flow oxygen is defined as oxygen delivered at < 6 L/minute
[f]High-flow oxygen is defined as oxygen delivered at ≥ 6 L/minute
[g]Riegler L et al. (2019)

Immune effector cell-associated neurotoxicity syndrome (ICANS)

Patients should be monitored for signs and symptoms of ICANS. Other causes of neurologic symptoms should be ruled out. If ICANS is suspected, manage according to the recommendations in Table 6.

Table 6 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	Treatment with dexamethasone[d] Consider non-sedating anti-seizure medicinal products (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	Treatment with dexamethasone[f] Consider non-sedating anti-seizure medicinal products (e.g., levetiracetam) until resolution of ICANS No concurrent CRS*:* • Anti-cytokine therapy not recommended For ICANS with concurrent CRS*:* • Treatment with dexamethasone[f] • 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: • any clinical seizure, focal or generalised 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]	Treatment with dexamethasone[g] • If no response, initiate methylprednisolone 1,000 mg/day Consider non-sedating anti-seizure medicinal products (e.g., levetiracetam) until resolution of ICANS No concurrent CRS*:* • Anti-cytokine therapy not recommended For ICANS with concurrent CRS*:* • Treatment with dexamethasone[g] o If no response, initiate methylprednisolone 1,000 mg/day • Choose immunosuppressant alternatives[e] to tocilizumab, if possible	Permanently discontinue epcoritamab

Grade[a]	Recommended therapy	Epcoritamab dose modification
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 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	Treatment with dexamethasone[g] • If no response, initiate methylprednisolone 1,000 mg/day Consider non-sedating anti-seizure medicinal products (e.g., levetiracetam) until resolution of ICANS No concurrent CRS*:* • Anti-cytokine therapy not recommended For ICANS with concurrent CRS*:* • Treatment with dexamethasone[g] o If no response, initiate methylprednisolone 1,000 mg/day • Choose immunosuppressant alternatives[e] to tocilizumab, if possible	Permanently discontinue epcoritamab

[a]ICANS graded 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 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)
[f]Dexamethasone 10-20 mg intravenously every 12 hours
[g]Dexamethasone 10-20 mg intravenously every 6 hours

Table 7 Recommended dose modifications for other adverse reactions when Tepkinly is given as monotherapy

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 • For Grade 4, consider permanent discontinuation of epcoritamab
Neutropenia or febrile neutropenia (see section 4.8)	Absolute neutrophil count less than 0.5 x 10^9/L	• Withhold epcoritamab until absolute neutrophil count is 0.5 x 10^9/L or higher
Thrombocytopenia (see section 4.8)	Platelet count less than 50 x 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.		

Table 8: Recommended Dosage Modifications for Other Adverse Reactions when Tepkinly is Given in Combination with Lenalidomide and Rituximab

Adverse Reaction	**Severity[1]**	**Action[2]**
Neutropenia (see section 4.8)	Absolute neutrophil count less than 0.5 x 10^9/L	• Consider G-CSF. • Withhold Tepkinly until absolute neutrophil count is 1 x 10^9/L or higher.[3] • Withhold lenalidomide for remainder of cycle. On Day 1 of next cycle, the dose of lenalidomide may be maintained if neutropenia was the only toxicity limiting lenalidomide dosing.
Febrile Neutropenia (see section 4.8)	Grade 3 or higher	• Consider G-CSF. • Withhold Tepkinly until fever resolves and absolute neutrophil count is 1 x 10^9/L or higher.[3] • Withhold lenalidomide for remainder of cycle. On Day 1 of next cycle, dose of lenalidomide may be maintained if febrile neutropenia was the only toxicity limiting lenalidomide dosing.

Adverse Reaction	Severity[1]	Action[2]
Thrombocytopenia (see section 4.8)	Platelet count less than 50 x 10^9/L	• Withhold Tepkinly until platelet count is 50 x 10^9/L or higher.[3] • Withhold lenalidomide for remainder of cycle. Decrease lenalidomide dose for next cycle.
Other Adverse Reactions (see section 4.8)	Grade 3	• For first episode, withhold Tepkinly until improvement to Grade 2 or less or resolution to baseline.[3] • For second episode, permanently discontinue Tepkinly if clinically indicated.[3]
	Grade 4	• Permanently discontinue Tepkinly at discretion of healthcare provider.
[1] Based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 5.0. [2] Refer to lenalidomide prescribing information for additional toxicity guidelines. [3] See below for recommendations on restarting Tepkinly after dosage delays.		

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).

Special populations

Renal impairment

Dose adjustments are not considered necessary in patients with mild to moderate renal impairment. Epcoritamab has not been studied in patients with severe renal impairment to end stage renal disease. No dose recommendations can be made for patients with severe renal impairment to end-stage renal disease (see section 5.2).

Hepatic impairment

Dose adjustments are not considered necessary in patients with mild hepatic impairment. Epcoritamab has not been studied in patients with severe hepatic impairment (defined as total bilirubin > 3 times ULN and any AST) and data are limited in patients with moderate hepatic impairment (defined as total bilirubin > 1.5 to 3 times ULN and any AST). No dose recommendations can be made for patients with moderate to severe hepatic impairment (see section 5.2).

Elderly

No dose adjustment is necessary in patients ≥ 65 years of age (see sections 5.1 and 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.

Method of administration

Tepkinly is for subcutaneous use. It should be administered by subcutaneous injection only, 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 or preparation 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)

CRS, which may be life-threatening or fatal, occurred in patients receiving epcoritamab. The most common signs and symptoms of CRS include pyrexia, hypotension and hypoxia. Other signs and symptoms of CRS in more than two patients 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, treatment should be instituted of supportive care with tocilizumab and/or corticosteroids as appropriate (see section 4.2, Table 5). Patients should be counselled on the signs and symptoms associated with CRS and patients should be instructed 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.

For patients with FL, assess whether hospitalization or outpatient monitoring for the first 48 mg dose (Cycle 1 Day 22) is appropriate based on comorbidities or other situational factors. During outpatient monitoring after the first 48 mg dose, patients should remain in proximity to a healthcare facility that can assess and manage 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. 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 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, treatment with corticosteroids and non-sedating-anti-seizure medicinal products should be instituted as appropriate (see section 4.2, Table 6). Patients should be counselled on the signs and symptoms of ICANS and that the onset of events may be delayed. Patients should be instructed to contact their healthcare professional and seek immediate medical attention should signs or symptoms occur at any time. Epcoritamab should be delayed or discontinued as recommended (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 ICANS.

Serious infections

Treatment with epcoritamab may lead to an increased risk of infections. Serious or fatal infections were observed in patients treated with epcoritamab in clinical studies (see section 4.8).

Administration of epcoritamab should be avoided in patients with clinically significant active systemic infections.
As appropriate, prophylactic antimicrobials should be administered prior to and during treatment with epcoritamab (see section 4.2). 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.

CD20-negative disease

There are limited data available on patients with CD20-negative DLBCL and patients with CD20-negative FL treated with epcoritamab, and it is possible that patients with CD20-negative DLBCL and patients with CD20-negative FL may have less benefit compared to patients with CD20-positive DLBCL and patients with CD20-positive FL, respectively. The potential risks and benefits associated with treatment of patients with CD20-negative DLBCL and FL with epcoritamab should be considered.

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 epcoritamab therapy. 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 28.8 mg of sorbitol per vial, which is equivalent to 27.33 mg/ml.

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.

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

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.

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 ICANS, patients receiving epcoritamab are at risk of altered level of consciousness (see section 4.4). Patients should be advised to exercise caution while (or avoid if symptomatic) driving, cycling or using heavy or potentially dangerous machines.

4.8 Undesirable effects

Summary of the safety profile

Epcoritamab monotherapy

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, injection site reactions, fatigue, viral infection, neutropenia, musculoskeletal pain, pyrexia and diarrhoea.

Serious adverse reactions occurred in 50% of patients. The most frequent serious adverse reaction (≥ 10%) was cytokine release syndrome (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, in 1 (0.3%) patient each.

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

Epcoritamab in combination with lenalidomide and rituximab

The safety of Tepkinly in combination with lenalidomide and rituximab was evaluated in EPCORE FL-1 (M20-638), an open-label, randomized, multicenter trial that included patients with relapsed or refractory FL after at least one line of systemic therapy. The study excluded patients with transformed lymphoma, absolute neutrophil count < 1.0 x 10^9/L, platelet count < 70 x 10^9/L (or < 50 x 10^9/L if bone marrow infiltration by lymphoma or splenomegaly), known active infection, creatinine clearance < 50 mL/min, alanine or aspartate transaminase > 3 times the upper limit of normal, and clinically significant cardiovascular disease. Patients were randomized to receive Tepkinly in combination with lenalidomide and rituximab (N=243) or lenalidomide and rituximab alone (N=238). Patients received Tepkinly via subcutaneous injection in 28-day cycles for a total of 12 cycles or until disease progression or unacceptable toxicity, whichever occurred first. Of the 243 patients who received Tepkinly, 131 received the recommended 3 step-up dosage schedule.

The recommended Tepkinly dosage schedule was:

- Cycle 1: Tepkinly 0.16 mg on Day 1, 0.8 mg on Day 8, 3 mg on Day 15, and 48 mg on Day 22
- Cycles 2-3: Tepkinly 48 mg on Days 1, 8, 15, and 22
- Cycles 4-12: Tepkinly 48 mg on Day 1

In both treatment arms, lenalidomide was given orally at a dose of 20 mg once daily from Days 1 to 21 for 12 cycles. Rituximab was administered intravenously at a dose of 375 mg/m^2 on Days 1, 8, 15, and 22 of Cycle 1, followed by administration on Day 1 of Cycles 2 to 5.

Safety results are based on all 243 patients who received Tepkinly, with the exception of data for CRS and ICANS which are based on patients who received Tepkinly at the recommended dosage schedule. The median duration of exposure in this arm was 10 cycles for Tepkinly and 9 cycles for lenalidomide.

Serious adverse reactions occurred in 51% of these patients, including serious infections in 28% of patients and serious CRS in 12% of patients. Fatal adverse reactions within 60 days of last treatment occurred in 0.8% of patients.

Adverse reactions led to permanent discontinuation of Tepkinly in 6% of patients and dose interruption in 75% of patients, with infection as a leading cause. Adverse reactions leading to interruption of Tepkinly in ≥ 5% of patients included respiratory tract infections, CRS, and rash.

In the Tepkinly arm, adverse reactions led to lenalidomide dose interruption in 72%, dose reduction in 22%, and permanent discontinuation in 15%.

The most common (≥ 20%) adverse reactions in the Tepkinly arm were rash, upper respiratory tract infections, fatigue, injection site reactions, constipation, diarrhea, CRS, pneumonia, COVID-19, and fever. The most common Grade 3 to 4 laboratory abnormalities (≥ 10%) were decreases in neutrophil count, lymphocyte count, and platelets.

Tabulated list of adverse reactions

Adverse reactions occurring with epcoritamab monotherapy in study GCT3013-01 are listed in Table 9.

Adverse reactions occurring with epcoritamab in combination with lenalidomide and rituximab in study EPCORE FL-1 (M20-638) are listed in Table 10 and Table 11.

Table 9 of Adverse reactions for epcoritamab from clinical studies is 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).
Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 9 Adverse reactions reported in patients with relapsed or refractory LBCL or FL treated with epcoritamab monotherapy in study GCT3013-01

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
Neoplasm benign, malignant and unspecified (including 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	Uncommon
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 papular, 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, generalised oedema, oedema, oedema peripheral, peripheral swelling, swelling, and swelling face
[t]Blood sodium decreased includes blood sodium decreased and hyponatraemia

Table 10: Adverse Reactions (≥ 10% All Grade and ≥ 5% Higher) in Patients with Relapsed or Refractory FL Who Received Tepkinly in Combination with Lenalidomide and Rituximab in EPCORE FL-1

Adverse Reaction[§]	Tepkinly + Lenalidomide and Rituximab		Lenalidomide and Rituximab	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
	(N=131)		(N=238)	
Immune system disorders				
Cytokine release syndrome	24[†*]	0	0.8	0
	(N=243)		(N=238)	
Skin and subcutaneous tissue disorders				
Rash[a]	46	11[#]	34	6[#]
Infections and infestations				
Upper respiratory tract infections[b]	33	3.3	18	0.4[#]
Pneumonia[c]	24	16[#]	8[††]	4.6
COVID-19[d]	23	5[#]	13	1.3[#]
General disorders and administration site conditions				
Fatigue[e]	31	4.9[#]	24	2.1[#]
Injection site reactions	27	0	0.4	0
Fever	23	0.4[#]	11	1.3[#]
Gastrointestinal disorders				
Constipation	26	0.8[#]	21	0
Mucositis[f]	12	0	3.4	0
Nervous system disorders				
Neurological changes[g]	15	1.2[#]	8	1.3[#]
Headache	11	0	3.8	0
Psychiatric disorders				
Insomnia	14	0	2.9	0

This table includes a combination of grouped and ungrouped terms.
[§] Adverse reactions were graded using CTCAE Version 5.0. CRS was graded using ASTCT consensus criteria (Lee et al., 2019).
[†] The frequency of CRS is based on 131 patients who received Tepkinly at the recommended dosage schedule (see section 4.2). Grade 1 CRS: 19%; Grade 2 CRS: 5%.

Adverse Reaction[§]	Tepkinly + Lenalidomide and Rituximab		Lenalidomide and Rituximab	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)

[*] The frequency of CRS among the 243 patients who received either the 2-step up or 3-step up dosage schedule was the following: Any grade CRS 35%; Grade 1 CRS: 28%; Grade 2 CRS: 7%.
[#] Only Grade 3 adverse reactions occurred.
[††] Includes one case with a fatal outcome.
[a] Rash includes blister, dermatitis, erythema, rash, skin exfoliation, skin reaction, toxic skin eruption, urticaria and related terms.
[b] Upper respiratory tract infections include sinusitis, laryngitis, nasopharyngitis, pharyngitis, rhinitis, rhinovirus infection, upper respiratory tract infection, and related terms.
[c] Pneumonia includes pneumonia, COVID-19 pneumonia, pneumonia fungal, Pneumocystis jirovecii pneumonia, pneumonia cytomegaloviral, and related terms.
[d] COVID-19 includes COVID-19, COVID-19 pneumonia, coronavirus infection, coronavirus pneumonia.
[e] Fatigue includes asthenia, fatigue, lethargy, malaise.
[f] Mucositis includes gingival pain, glossitis, mouth ulceration, mucosal infection, mucosal inflammation, oral discomfort, oral mucosal exfoliation, oropharyngeal pain, stomatitis.
[g] Neurological changes include brain fog, cognitive disorder, confusional state, disturbance in attention, dysphonia, epilepsy, essential tremor, gait disturbance, hypoacusis, lethargy, loss of consciousness, memory impairment, somnolence, syncope, tremor, vertigo, and ICANS.

Other clinically relevant adverse reactions include:
Gastrointestinal disorders: diarrhea (26%), nausea (16%), abdominal pain (11%), vomiting (4.1%)
Musculoskeletal and connective tissue disorders: musculoskeletal pain (14%), arthralgia (8%)
Nervous system disorders: peripheral neuropathy (12%), dizziness (7%), ICANS (0.8%)
General disorders: edema (12%)
Infections: cytomegalovirus infection (7%), herpesvirus infection (7%), sepsis (2.9%)
Blood and lymphatic system disorders: febrile neutropenia (6%)
Neoplasms: tumor flare (1.2%)

Table 11 summarizes laboratory abnormalities in EPCORE FL-1. Grade 4 laboratory abnormalities in ≥ 2% of the Tepkinly arm included decreases in neutrophils (41%), lymphocytes (13%), and platelets decreased (4.1%).

Table 11: Select Laboratory Abnormalities (≥ 30% All Grade and ≥ 10% Higher) That Worsened from Baseline in Patients with Relapsed or Refractory FL Who Received Tepkinly in Combination with Lenalidomide and Rituximab in EPCORE FL-1

Laboratory Abnormality	Tepkinly + Lenalidomide and Rituximab[1]		Lenalidomide and Rituximab[1]	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Hematology				
Neutrophils decreased	86	67	75	41
Lymphocytes decreased	86	62	56	15
Hemoglobin decreased	66	7	52	4.7
Platelets decreased	50	10	37	7

Chemistry				
Alanine aminotransferase increased	58	7	36	0.9
Phosphate decreased[2]	49	N/A	28	N/A
Sodium decreased	43	4.1	23	2.6
Potassium decreased	41	9	20	4.7
Aspartate aminotransferase increased	40	2.9	29	0.9

Laboratory abnormalities were graded based on CTCAE Version 5.0
[1] The denominator used to calculate the rate varied from 240 to 242 in the Tepkinly arm, and 225 to 236 in the comparator arm, based on the number of patients with a baseline value and at least one post-treatment value.
[2] CTCAE Version 5.0 does not include numeric thresholds for grading of hypophosphatemia; all grades represent patients with lab value < Lower Limit of Normal (LLN).

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. 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 to 7 days). CRS resolved in 99% of patients, and the median duration of CRS events was 2 days (range 1 to 54 days).

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%). Transient elevated liver enzymes (ALT or AST > 3xULN) were concurrent with CRS in 4.1% of patients with CRS. See section 4.2 and 4.4 for monitoring and management guidance.

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%, 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.

Epcoritamab in combination with lenalidomide and rituximab

CRS occurred in 24% (32/131) of patients with FL receiving Tepkinly at the recommended dosage schedule in combination with lenalidomide and rituximab in EPCORE FL-1, with Grade 1 CRS occurring in 19%, Grade 2 in 5% of patients, and serious adverse reactions due to CRS in 12%. Recurrent CRS occurred in 41% of patients. Most CRS events (88%) occurred during Cycle 1. In Cycle 1, CRS occurred in 5% of patients after the 0.16 mg dose, 3.8% after the 0.8 mg dose, 2.3% after the 3 mg dose, and 18% after the first 48 mg dose. The median time to onset of CRS from the most recent Tepkinly dose was 78 hours (range: 0.2 to 12 days). The median time to onset after the first 48 mg dose was 41 hours (range: 0.3 to 12 days).

Immune effector cell-associated neurotoxicity syndrome

Epcoritamab monotherapy

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). In the 18 patients with ICANS, the onset of ICANS was prior to CRS in 11% of patients, concurrent with CRS in 44%, following onset of CRS in 17%, and in the absence of CRS in 28%.

Epcoritamab in combination with lenalidomide and rituximab
Among patients with FL who received Tepkinly at the recommended dosage schedule in combination with lenalidomide and rituximab in EPCORE FL-1, ICANS occurred in 0.8% (1/131, Grade 1).

Serious infections

Epcoritamab monotherapy

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 included COVID-19 (6.6%), COVID-19 pneumonia (4.2%), pneumonia (3.6%), sepsis (2.4%), upper respiratory tract infection (1.8%), bacteraemia (1.2%), and septic shock (1.2%). The median time to onset of first serious infection from the start of epcoritamab treatment (Cycle 1 Day 1) was 56 days (range: 4 to 631 days), with median duration of 15 days (range: 4 to 125 days). Grade 5 events of infections occurred in 7 (4.2%) patients.

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.

Epcoritamab in combination with lenalidomide and rituximab

Among 243 patients with FL who received Tepkinly in combination with lenalidomide and rituximab in EPCORE FL-1, serious infections occurred in 28% of patients. The most common serious infections were pneumonia (15%), COVID-19 (7%), opportunistic infections (5%) and upper respiratory infections (3.3%). The most common opportunistic infections of any grade were CMV infection (7%) and herpesvirus infection (7%).

Neutropenia

Epcoritamab monotherapy

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.

Epcoritamab in combination with lenalidomide and rituximab

In patients with FL who received Tepkinly in combination with lenalidomide and rituximab, Grade 3 or 4 decreased neutrophils occurred in 67% (Grade 4, 41%), decreased lymphocytes in 62% (Grade 4, 13%), decreased hemoglobin in 7%, and decreased platelets in 10% (Grade 4, 4.1%) of patients. Febrile neutropenia occurred in 6% (Grade 4, 2.1%).

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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form:

https://sideeffects.health.gov.il

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. 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.

Epcoritamab Fc region is silenced to prevent target-independent immune effector mechanisms, such as antibody-dependent cellular cytotoxicity (ADCC), complement-dependent cellular cytotoxicity (CDC), and antibody-dependent cellular phagocytosis (ADCP).
In nonclinical studies, the combination of epcoritamab-bysp and rituximab resulted in both T-cell mediated cytotoxicity and natural killer (NK) cell mediated antibody-dependent cellular cytotoxicity (ADCC).

Pharmacodynamic effects

Epcoritamab induced rapid and sustained depletion of circulating B-cells (defined as CD19 B-cell counts ≤ 10 cell/µl) in the subjects who have detectable B cells at treatment initiation. There were 21% subjects (n=33) with DLBCL and 50% subjects (n=56) with FL who had detectable circulating B-cells at treatment initiation. Transient reduction in circulating T cells was observed immediately after each dose in Cycle 1 and followed by T cell expansion in subsequent cycles.

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 post dose. Cytokine levels returned to baseline prior to the next full dose, however elevations of cytokines could also be observed after Cycle 1.
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.

Immunogenicity

Anti-drug antibodies (ADA) were commonly detected. 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.

Anti epcoritamab-bysp antibodies developed in 2.1% of patients (5 of 236) with FL treated with Tepkinly in combination with lenalidomide and rituximab in EPCORE FL 1 (up to 12 cycles) using an ECLIA.

No evidence of ADA impact on pharmacokinetics, efficacy or safety was observed, however, data are still limited. Neutralising antibodies were not evaluated.

Clinical efficacy and safety

Diffuse large B-cell lymphoma

Study GCT3013-01 was an open-label, multi-cohort, multicentre, single-arm study that evaluated epcoritamab as monotherapy in patients with relapsed or refractory large B-cell lymphoma (LBCL) after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL). The study includes a dose escalation part and an expansion 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 aNHL cohort consisted of patients with LBCL (N=157), including patients with DLBCL (N=139, 12 patients of which had MYC, BCL2, and/or BCL6 rearrangements i.e., DH/TH), with high-grade B-cell lymphoma (HGBCL) (N=9), with follicular lymphoma grade 3B (FL) (N=5) and patients with primary mediastinal B-cell lymphoma (PMBCL) (N=4). In the DLBCL cohort, 29% (40/139) of patients had transformed DLBCL arising from indolent lymphoma. 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, 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 central nervous system (CNS) involvement of lymphoma, prior treatment with 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, cardiac ejection fraction less than 45%, and known clinically significant cardiovascular disease. Efficacy was evaluated in 139 patients with DLBCL who had received at least one dose of epcoritamab SC in cycles of 4 weeks, i.e., 28 days. Epcoritamab monotherapy was administered at the recommended 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 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 12.

Table 12 Demographics and baseline characteristics of patients with DLBCL in GCT3013-01 study

Characteristics	**(N=139)**
Age	
Median, years (min, max)	66 (22, 83)
< 65 years, n (%)	66 (47)
65 to < 75 years, n (%)	44 (32)
≥ 75 years, n (%)	29 (21)
Males, n (%)	85 (61)
Race, n (%)	
White	84 (60)
Asian	27 (19)
Other	5 (4)
Not Reported	23 (17)
ECOG performance status; n (%)	
0	67 (48)
1	67 (48)
2	5 (4)
Disease stage[c] at initial diagnosis, n (%)	
III	16 (12)
IV	86 (62)
Number of prior lines of anti-lymphoma therapy	
Median (min, max)	3 (2, 11)
2, n (%)	41 (30)
3, n (%)	47 (34)
≥ 4, n (%)	51 (37)
DLBCL Disease history; n (%)	
De Novo DLBCL	97 (70)
DLBCL transformed from indolent lymphoma	40 (29)
FISH Analysis Per Central lab[d], N=88	
Double-hit/Triple-hit lymphoma, n (%)	12 (14)
Prior autologous HSCT	26 (19)
Prior therapy; n (%)	
Prior CAR-T	53 (38)
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 the patient is refractory to frontline anti-lymphoma therapy.
[b]A patient is considered to be refractory if the patient either experiences disease progression during therapy or disease progression within < 6 months after therapy completion. A patient is considered relapsed if the patient had recurred disease ≥ 6 months after therapy completion.
[c]Per Ann Arbor Staging.
[d]Post hoc central lab FISH analysis was performed on available diagnostic baseline tumour tissue sections from 88 DLBCL patients.

The primary efficacy endpoint was 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). The median duration of exposure was 4.1 months (range: 0 to 23 months).

Table 13 Efficacy results in study GCT3013-01 in patients with DLBCL[a]

Endpoint **IRC assessment**	**Epcoritamab** **(N=139)**
ORR[b], n (%)	86 (62)
(95% CI)	(53.3, 70)
CR[b], n (%)	54 (39)
(95% CI)	(30.7, 47.5)
PR, n (%)	32 (23)
(95% CI)	(16.3, 30.9)
DOR[b]	
Median (95% CI), months	15.5 (9.7, NR)
DOCR[b]	
Median (95% CI), months	NR (12.0, NR)
TTR, median (range), months	1.4 (1, 8.4)

CI = confidence interval; CR = complete response; DOR = duration of response; DOCR = duration of complete response; IRC = independent review committee; ORR = overall response rate; PR = partial response; 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 2.6 months (range: 1.2 to 10.2 months).

Follicular lymphoma

EPCORE FL-1

The efficacy of Tepkinly in combination with lenalidomide and rituximab was evaluated in EPCORE FL-1 (Study M20-638; NCT05409066), an open-label, randomized, multicenter, global trial in patients with relapsed or refractory FL after at least one line of systemic therapy. Patients were randomized to receive Tepkinly in combination with lenalidomide and rituximab, or lenalidomide and rituximab alone. The study excluded patients with known CNS involvement by lymphoma, prior allograft, and known

active infection. Patients received Tepkinly via subcutaneous injection in 28-day cycles for a total of 12 cycles or until disease progression or unacceptable toxicity, whichever occurred first.

The recommended Tepkinly dosage schedule was:

- Cycle 1: Tepkinly 0.16 mg on Day 1, 0.8 mg on Day 8, 3 mg on Day 15 and 48 mg on Day 22
- Cycles 2-3: Tepkinly 48 mg on Days 1, 8, 15, and 22
- Cycles 4-12: Tepkinly 48 mg on Day 1

In both treatment arms, lenalidomide was given orally at a dose of 20 mg once daily from Days 1 to 21 for 12 cycles and Rituximab was administered intravenously at a dose of 375 mg/m^2 on Days 1, 8, 15, and 22 of Cycle 1, followed by administration on Day 1 of Cycles 2 to 5.

Of all patients randomized, the median age was 61 years (range: 24 to 89 years), with 40% being age 65 or older; 57% were male; 72% were White, 24% Asian, and 2% were Black; and 98% had an ECOG performance status of 0 or 1. The median number of prior lines of systemic therapy was 1 (range: 1 to 7) with 24% receiving 2 prior lines and 17% receiving 3 or more prior lines of therapy. Forty-one percent had progressive disease within 24 months of first systemic therapy.

Efficacy was established based on progression free survival (PFS) and overall response rate (ORR) as assessed by Independent Review Committee (IRC) using Lugano 2014 criteria.

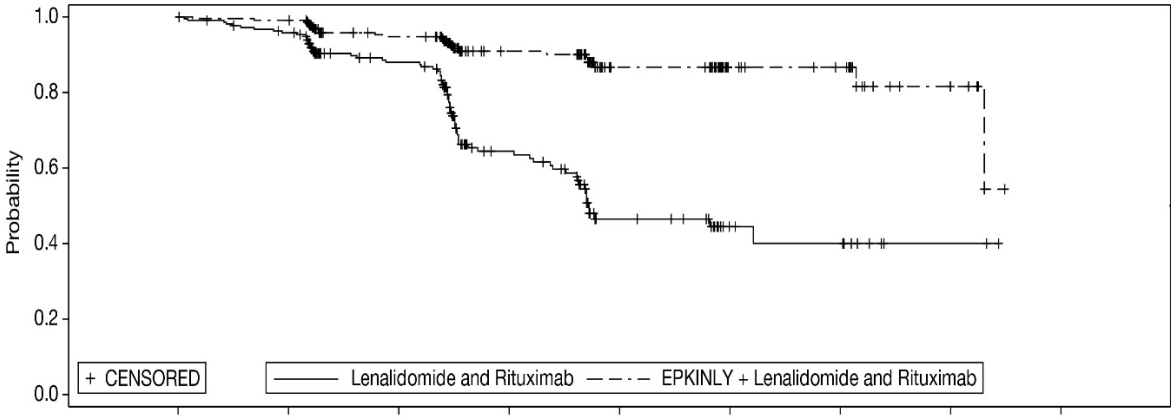
The efficacy results, based on a prespecified interim analysis, are summarized in Table 19 and the Kaplan-Meier plot of PFS presented in Figure 1. The results are based on a median duration of follow-up of 10.4 months in the intention-to-treat population.

Table 14: Efficacy Results in EPCORE FL-1 in Patients with FL

Outcome per IRC	**Tepkinly + Lenalidomide and Rituximab (N=243)**	**Lenalidomide and Rituximab (N=245)**
PFS		
Number of events, n (%)	23 (9)	75 (31)
Progressive disease	19 (83)	63 (84)
Death	4 (17)	12 (16)
Median (95% CI), months	NR (21.9, NR)	11.2 (10.5, NR)
Hazard ratio[a] (95% CI)	0.21 (0.13, 0.33)	
P-value[b]	< 0.0001	
ORR, n (%)	216 (89)	181 (74)
(95% CI)	(84, 93)	(68, 79)
P-value[c,d]	< 0.0001	
CR, n (%)	181 (74)	106 (43)
(95% CI)	(69, 80)	(37, 50)
P-value[d]	< 0.0001	

PFS = progression free survival; CI = confidence interval; NR = not reached; ORR = overall response rate; CR = complete response.
[a] Cox proportional hazards hazard ratio stratified by disease history and region.
[b] Log-rank p-value (one sided) stratified by disease history and region.
[c] P-value is based on a prespecified analysis of the first 232 patients randomized.
[d] P-value (one sided) is from a Cochran-Mantel-Haenszel test stratified by disease history and region.

Figure 1: Kaplan-Meier Plot of PFS per IRC



N of subjects at risk									
Lenalidomide and Rituximab	245	203	149	68	28	11	9	2	0
EPKINLY + Lenalidomide and Rituximab	243	224	182	103	57	29	24	8	0

After a median duration of follow-up of 14.8 months overall, the median overall survival had not been reached in either arm with a total of 35 deaths: 10 (4%) deaths in the Tepkinly arm and 25 (10%) deaths in the lenalidomide and rituximab arm.

GCT3013-01

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 15.

Table 15 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)
Prior Therapy; n (%)	
Autologous stem cell transplant	24 (19)
Chimeric antigen receptor (CAR)-T cell therapy	6 (5)
Rituximab plus lenalidomide therapy	27 (21)

Characteristics	**(N = 128)**
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 16.

Table 16 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).

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 C_{trough} at Week 12 is 8.4 (53.3%) mcg/ml.

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 C_{trough} for q2W schedule is 4.1 (73.9%) mcg/ml.

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. The C_{trough} for q4W schedule is 1.2 (130%) mcg/ml.

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%) and apparent steady-state volume of distribution is 25.6 l (81.8%) 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 (Cycle 1 AUC within approximately 36%) were observed based on age (20 to 89 years), sex, or race/ethnicity (white, Asian, and other), mild to moderate renal impairment creatinine clearance (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.

Like other therapeutic proteins, body weight (39 to 172 kg) has a statistically significant effect on the pharmacokinetics of epcoritamab. Based on exposure-response analysis and clinical data, considering the exposures in patients at either low body weight (e.g., 46 kg) or high body weight (e.g., 105 kg) and across body weight categories (< 65 kg, 65-< 85, ≥ 85), the effect on exposures is not clinically relevant.

In patients with relapsed or refractory FL who received Tepkinly in combination with lenalidomide and rituximab in EPCORE FL-1, 88 (36%) were 65 years of age or older and 20 (8%) were 75 years of age or older. No clinically meaningful differences in safety or efficacy were observed between patients who were 65 years of age and older compared with younger patients.

Paediatric population

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

5.3 Preclinical safety data

Animal pharmacology and/or toxicology

No reproductive or developmental toxicity studies in animals have been conducted with epcoritamab. 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.

Mutagenicity

Mutagenicity studies have not been conducted with epcoritamab.

Carcinogenicity

Carcinogenicity 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. The AUC exposures (time-averaged over 7 days) at the high dose in cynomolgus monkeys were similar to those in patients (AUC0-7d) receiving the recommended dose.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

D-Sorbitol
Sodium acetate trihydrate
Polysorbate 80
Acetic acid, glacial
Water for injection

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

The expiry date of the product is indicated on the packaging materials.

Tepkinly 4 mg/0.8 ml

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 dilution 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.

Tepkinly 48 mg

Prepared epcoritamab **(No dilution required)**
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).
Do not freeze.
Keep the vial in the outer carton in order to protect from light.

Tepkinly 4 mg/0.8 ml
For storage conditions after dilution/first opening of the medicinal product, see section 6.3.

Tepkinly 48 mg
For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

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

Tepkinly 48 mg
Type I glass vial with a bromobutyl rubber stopper coated with fluoropolymer at the contact site and aluminium seal with a plastic orange flip off cap, containing 48 mg per 0.8 ml solution for injection.

Each carton contains one vial.

6.6 Special precautions for disposal and other handling

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 foreign particles are present.
Tepkinly 4 mg/0.8 ml

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 has to be prepared using aseptic technique. Filtration of the diluted solution is not required.

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 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 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 second dilution a) Label an appropriately sized empty vial as **"dilution B"**. b) Transfer **2 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 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 dose Withdraw **1 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 syringe Label the syringe with the product name, 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 and any unused portion of epcoritamab in accordance with local requirements.

0.8 mg intermediate dose preparation instructions – **1 dilution required– empty sterile vial method**
Use an appropriately sized syringe, vial 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 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 – 45 seconds.
3) Withdraw dose Withdraw **1 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 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 and any unused portion of epcoritamab in accordance with local requirements.

Preparation of diluted epcoritamab using the sterile syringe method

0.16 mg priming dose preparation instructions - **2 dilutions required – sterile syringe method**
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.

0.8 mg intermediate dose preparation instructions - **1 dilution required – sterile syringe method**
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.

Preparation of 3 mg epcoritamab dose

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.

Tepkinly 48 mg

48 mg full dose preparation instructions - **No dilution required**

Tepkinly 48 mg vial is supplied as ready-to-use solution that does not need dilution prior to administration.

Epcoritamab has to be prepared using aseptic technique. Filtration of the solution is not required

1) Prepare epcoritamab vial a) Retrieve one 48 mg epcoritamab vial with the **orange** 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 **0.8 ml of epcoritamab** into a syringe.
3) Label syringe Label the syringe with the product name, dose strength (48 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. MANUFACTURER

AbbVie Deutschland GmbH & Co. KG, Knollstrasse, 67061 Ludwigshafen, Germany

8. LICENSE HOLDER

AbbVie biopharmaceuticals LTD., 4 Hacharash St., Hod Hasharon, Israel

9. REGISTRATION NUMBER

176-08-37756
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