Summary Report of Benefit-Risk Assessment

EPKINLY CONCENTRATE FOR SOLUTION FOR INJECTION 4MG/0.8ML, EPKINLY SOLUTION FOR INJECTION 48MG/0.8ML

NEW DRUG APPLICATION

Active Ingredient(s)	Epcoritamab
Product Registrant	Abbvie Pte. Ltd.
Product Registration Number	SIN17105P, SIN17106P
Application Route	Abridged evaluation
Date of Approval	02 October 2024

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A INTRODUCTION

Epkinly is indicated for the treatment of adult patients with relapsed or refractory (R/R) diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy.

The active substance, 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.

Epkinly is available as solution for injection containing 4mg/0.8ml of epcoritamab or concentrate for solution for injection containing 48mg/0.8ml of epcoritamab. Other ingredients in the vial are sodium acetate trihydrate, acetic acid, D-sorbitol, polysorbate 80 and water for injection.

B ASSESSMENT OF PRODUCT QUALITY

The drug substance, epcoritamab, is manufactured at Rentschler Biopharma Inc., MA, USA. The drug product, Epkinly, is manufactured at Vetter Pharma-Fertigung GmbH & Co. KG, Langenargen, Germany.

Drug substance:

Adequate controls have been presented for the starting materials, intermediates, and cell banks. The in-process control tests and acceptance criteria applied during the manufacturing of the drug substance are considered appropriate. The drug substance manufacturer is compliant with Good Manufacturing Practice (GMP) standard. Process validation was conducted on three consecutive production-scale batches.

The characterisation of the drug substance and its impurities has been appropriately performed. Potential and actual impurities are adequately controlled in the specifications.

The drug substance specifications were established in accordance with ICH Q6B guideline and the impurity limits have been considered appropriately qualified. The analytical methods used were adequately described and non-compendial methods have been validated in accordance with ICH Q2 guideline, with information on the reference standards used for identity, assay and impurities testing presented.

The stability data presented was adequate to support the storage of the drug substance at ≤-60°C with a shelf life of 30 months. The packaging is single use sterile 5L low-density polyethylene (LDPE) bags.

Drug product:

The manufacturing process involves pooling and homogenisation of the formulated drug substance, followed by pre-filtration, sterile filtration and aseptic filling. This is considered a standard manufacturing process.

The manufacturing site is compliant with GMP standard. Proper development and validation studies were conducted. It has been demonstrated that the manufacturing process is reproducible and consistent. Adequate in-process controls are in place.

The specifications were established in accordance with ICH Q6B guideline and impurity limits are considered adequately qualified. The analytical methods used were adequately described and non-compendial methods have been validated in accordance with ICH Q2 guideline, with information on the reference standards used for identity, assay and impurities testing presented.

The stability data submitted was adequate to support the approved shelf-life of 24 months when stored between 2°C and 8°C. The container closure system is a 2R, clear, type I, borosilicate glass vial with bromobutyl rubber stopper and aluminium cap with orange polypropylene flip-off disc.

C ASSESSMENT OF CLINICAL EFFICACY

The clinical efficacy of epcoritamab in the treatment of adult patients with R/R DLBCL after two or more lines of systemic therapy was based primarily on data from one pivotal study, GCT3013-01, which was a Phase I/II, open-label, single-arm study in patients with R/R B-cell lymphoma who had received at least two prior systemic therapies.

The study included a Dose Escalation Part and an Expansion Part consisting of 3 cohorts: aggressive B-cell non-Hodgkin lymphoma (aNHL) (referred to as large B-cell lymphoma [LBCL]), indolent B-cell non-Hodgkin lymphoma (iNHL), and mantle cell lymphoma (MCL). The data from the aNHL cohort provided the pivotal evidence in support of the application. Patients included in the aNHL expansion cohort were aged 18 years or older and had documented CD20+ mature B-cell neoplasm according to World Health Organization (WHO) classification 2016 or WHO classification 2008 based on representative pathology report. Subjects must have been diagnosed with DLBCL (de novo or transformed from all indolent subtypes including Richter's transformation), including subjects diagnosed with double-hit or triple-hit DLBCL, with MYC and BCL2 and/or BCL6 rearrangements, or other LBCL subtypes (including primary mediastinal large B-cell lymphoma [PMBCL], high-grade B-cell lymphoma [HGBCL], or follicular lymphoma grade 3B [FL3B]). Subjects must have had relapsed or refractory disease and previously been treated with at least two lines of systemic antineoplastic therapy, including at least one anti-CD20 monoclonal antibody-containing therapy. Subjects also must have failed prior autologous stem cell transplantation (ASCT) or were ineligible for ASCT due to age, ECOG performance status, comorbidities, and/or insufficient response to prior treatment.

The dosing regimen of epcoritamab in the Expansion Part included a priming dose of 0.16 mg (Cycle 1 Day 1), an intermediate dose of 0.8 mg (Cycle 1 Day 8), and a full dose of 48 mg (Cycle 1 Day 15, Cycle 1 Day 22, and thereafter), administered subcutaneously according to the following schedule:

- Cycles 1 to 3: Days 1, 8, 15, and 22 (every week)
- Cycles 4 to 9: Days 1 and 15 (every 2 weeks)
- Cycle 10 and beyond until unacceptable toxicity, progressive disease, or withdrawal of consent: Day 1 (every 4 weeks)

The primary efficacy endpoint was overall response rate (ORR) (partial response [PR] + complete response [CR]) determined by Lugano criteria as assessed by Independent Review

Committee (IRC). The secondary efficacy endpoints included duration of response (DOR), CR rate, duration of complete response (DOCR), progression-free survival (PFS), time to response (TTR), overall survival (OS), time to next (anti-lymphoma) therapy (TTNT), rate of minimal residual disease (MRD) negativity, and changes in lymphoma symptoms as measured by the Functional Assessment of Cancer Therapy – Lymphoma (FACT-Lym) questionnaire.

No formal hypothesis testing was performed. Assuming a non-evaluable rate of 10%, a sample size of 128 patients with DLBCL was estimated to provide approximately 90% power to detect the alternative hypothesis of at least 50% ORR while ensuring a 2-sided significance level of 0.05 using one-sample exact binomial test under the null hypothesis of at most 35% ORR.

As of the data cut-off date of 31 January 2022, a total of 157 patients with LBCL received at least one dose of epcoritamab in the pivotal aNHL cohort. Of these 157 patients, 139 patients had DLBCL (including 97 with de novo disease, 40 with transformed disease and 2 with unknown type), 9 patients had HGBCL, 5 patients had FL3B, and 4 patients had PMBCL. Of the patients enrolled as having DLBCL, 12 patients had tumours with MYC and BCL2 and/or BCL6 rearrangements (i.e., double-hit or triple-hit DLBCL) based on central laboratory fluorescence in situ hybridization (FISH) analysis.

More than half of the patients with LBCL (59.9%) were male. The median age was 64.0 years (range: 20, 83), with 48 (30.6%) patients aged 65 to <75 years, and 29 (18.5%) patients aged ≥75 years. More than half of patients were white (61.1%) and 19.1% of patients were Asian.

The patients were representative of the target patient population who were heavily pre-treated and generally refractory to prior therapies. The median number of prior lines of anti-lymphoma therapy was 3.0 (range: 2, 11), with 50 (31.8%) patients having received 3 prior lines of therapy and 61 (38.9%) patients having received ≥4 prior lines of therapy. A total of 31 (19.7%) patients had a prior ASCT and 61 (38.9%) patients had received prior chimeric antigen receptor T-cell (CAR T-cell) therapy, of which, 46 were refractory to CAR T-cell therapy. Over half of patients (61.1%) had primary refractory disease and 75.8% of patients were refractory to ≥2 consecutive prior lines of lymphoma therapy. Most patients (82.8%) were refractory to the last line of systemic antineoplastic therapy.

Summary of key efficacy results

	LBCL (N=157)	**DLBCL (N=139)**
Primary efficacy endpoint		
ORR, n (%)[a] (95% CI)	99 (63.1%) (55.0, 70.6)	86 (61.9%) (53.3, 70.0)
Secondary efficacy endpoints		
CR rate, n (%)[a] (95% CI)	61 (38.9%) (31.2, 46.9)	54 (38.8%) (30.7, 47.5)
DOR, median (months)[a] (95% CI)	12.0 (6.6, NR)	12.0 (6.6, NR)
DOCR, median (months)[a] (95% CI)	12.0 (9.7, NR)	12.0 (9.7, NR)
PFS[a] Number of events (%) Median PFS (months) (95% CI)	 90 (57.3%) 4.4 (3.0, 7.9)	 80 (57.6%) 4.4 (3.0, 8.2)
TTR, median (months)[a] (Min, max)	1.4 (1.0, 8.4)	1.4 (1.0, 8.4)
OS Number of events (%) Median (months)	 61 (38.9%) NR	 56 (40.3%) NR

(95% CI)	(11.3, NR)	(11.3, NR)
TTNT, median (months) (95% CI)	7.4 (5.9, 10.8)	8.2 (6.0, 13.9)

[a] Determined by Lugano criteria as assessed by IRC

As of the data cut-off date of 31 January 2022, the median duration of follow-up was 10.7 months (range: 0.3, 17.9) in patients with LBCL and 11.0 months (range: 0.3, 17.9) in patients with DLBCL. In LBCL patients (N=157), the ORR was 63.1% (95% confidence interval [CI]: 55.0, 70.6) with a CR rate of 38.9% and PR rate of 24.2% as assessed by IRC using Lugano criteria. In DLBCL patients (N=139), the ORR was 61.9% (95% CI: 53.3, 70.0) with 38.8% and 23.0% of patients achieving best response of CR and PR, respectively.

The subgroup analyses of ORR showed generally consistent results across subgroups, including those with high-risk features, such as patients with primary refractory disease, patients who had prior ASCT, patients who had prior CAR T-cell therapy, patients with advanced disease (Stage III/IV), and patients with transformed disease.

The median DOR was 12.0 months (95% CI: 6.6, not reached [NR]) in both LBCL and DLBCL patients. Response to epcoritamab generally occurred early, with median TTR of 1.4 months (range: 1.0, 8.4) in both LBCL and DLBCL patients.

In the HGBCL subgroup (N=21) [including HGBCL not otherwise specified (N=9) and HGBCL with MYC and BCL2 and/or BCL6 rearrangements (i.e., double-hit or triple-hit DLBCL) (N=12)], the ORR was 47.6% (95% CI: 25.7, 70.2), the CR rate was 28.6% (95% CI: 11.3, 52.2), and the median DOR was 12.0 months (95% CI: 1.1, NR).

The median PFS was 4.4 months (95% CI: 3.0, 7.9) in LBCL patients and 4.4 months (95% CI: 3.0, 8.2) in DLBCL patients. The median OS was not reached (95% CI: 11.3, NR) in both LBCL and DLBCL patients. The median TTNT was 7.4 months (95% CI: 5.9, 10.8) in LBCL patients and 8.2 months (95% CI: 6.0, 13.9) in DLBCL patients. The median duration of MRD negativity was not reached in both LBCL and DLBCL patients who were MRD-evaluable. In terms of patient-reported outcomes (PROs), the data generally demonstrated improvements in the FACT-Lym questionnaire subscales.

There were limitations with the early phase, single-arm study, which did not allow meaningful interpretation of the time-to-event endpoints such as PFS and OS. Nevertheless, the responses and duration of response observed with epcoritamab in DLBCL patients were considered clinically meaningful and compared favourably with other available drug therapies which have been approved for DLBCL in similar disease setting based on single-arm studies with similar sample sizes. Therefore, the data provided reasonable evidence to support the efficacy of epcoritamab for the treatment of adult patients with R/R DLBCL after two or more lines of systemic therapy.

For the HGBCL subgroup (N=21), while the results observed were promising and generally consistent with the overall population, given the very limited sample size, there were uncertainties on whether the observed effect size in the HGBCL subgroup was reflective of the true efficacy and whether it could translate into actual clinical benefit. The limited data based on the small sample size did not allow a conclusion to be drawn on the benefit-risk in this population to support a specific indication for HGBCL.

In order to confirm the clinical benefit and a favourable overall risk-benefit of epcoritamab, the approval of epcoritamab is subject to the condition attached to the product registration for the

company to submit the final results of Study GCT3013-01 and Study GCT3013-05, which is a Phase III study comparing the efficacy of epcoritamab to standard of care immunochemotherapy (i.e., rituximab with gemcitabine and oxaliplatin or bendamustine and rituximab) in patients with R/R DLBCL treated with at least one prior line of therapy.

D ASSESSMENT OF CLINICAL SAFETY

The safety data supporting the use of epcoritamab for the treatment of R/R DLBCL after two or more lines of systemic therapy was based on the primary safety analysis set (N=167) (referred to as the Safety Pool 01 LBCL group), which included all patients with LBCL who were assigned to receive the 48 mg full dose of epcoritamab and received at least 1 dose of epcoritamab in the Dose Escalation (N=10) and Expansion Parts (N=157) of Study GCT3013-01.

The median duration of treatment was 3.7 months (range: 0, 20) and the median number of cycles of treatment initiated per subject was 5.0 (range: 1, 22). A total of 53 (31.7%) patients continued to receive epcoritamab treatment as of the data cut-off date of 31 January 2022.

Overview of safety profile

	Safety Pool 01 LBCL group (N=167)
TEAE	166 (99.4%)
Grade ≥3 TEAE	105 (62.9%)
Treatment-related TEAE	140 (83.8%)
Grade ≥3 treatment-related TEAE	47 (28.1%)
Serious TEAE	97 (58.1%)
TEAE leading to treatment discontinuation	13 (7.8%)
Fatal TEAE	12 (7.2%)

Treatment-emergent adverse events (TEAEs) were reported in 166 (99.4%) patients. The most common (≥10%) TEAEs included cytokine release syndrome (CRS) (50.3%), fatigue (24.6%), pyrexia (22.8%), injection site reaction (22.2%), neutropenia (22.2%), nausea (20.4%), diarrhoea (19.8%), anaemia (18.0%), abdominal pain (13.8%), thrombocytopenia (13.2%), headache (12.6%), constipation (12.0%), vomiting (12.0%), decreased appetite (11.4%), oedema peripheral (11.4%), back pain (10.8%), and insomnia (10.8%).

Treatment-related TEAEs were reported in 140 (83.8%) patients and grade 3 or higher treatment-related TEAEs were reported in 47 (28.1%) patients. Treatment-related TEAEs reported in ≥10% of patients included CRS (50.3%), injection site reaction (22.2%), neutropenia (18.0%), fatigue (15.0%), and pyrexia (11.4%). Grade 3 or higher treatment-related TEAEs reported in ≥2% of patients included neutropenia (11.4%), neutrophil count deceased (3.6%), anaemia (2.4%), and CRS (2.4%).

A total of 97 (58.1%) patients experienced serious TEAEs. Serious TEAEs experienced by ≥2% of patients included CRS (31.1%); pleural effusion (4.8%); febrile neutropenia, immune effector cell-associated neurotoxicity syndrome (ICANS), pneumonia, pyrexia, and sepsis (2.4% each).

TEAEs leading to treatment discontinuation were reported in 13 (7.8%) patients. TEAEs leading to treatment discontinuation reported in more than 1 patient included COVID-19, COVID-19 pneumonia, and myelodysplastic syndrome (MDS) (attributed to prior therapy) in 2 (1.2%) patients each.

Fatal TEAEs were reported for 12 (7.2%) patients. One fatal TEAE of ICANS was considered related to epcoritamab by the investigator. All other fatal TEAEs were attributed to disease progression, COVID-19, or existing comorbidities/impact of prior therapies.

Adverse events of clinical importance included injection-related reactions, CRS, ICANS, tumour lysis syndrome (TLS), neutropenia, and infections. Injection site reactions were experienced by 50 (29.9%) patients, and all were grade 1 or 2 in severity.

CRS was reported in 84 (50.3%) patients. Almost all patients (80 out of 84 patients) experienced a maximum of grade 1 or 2 event and there were no grade 4 or 5 events of CRS reported. All cases of CRS resolved except for 2 patients. Only one patient (0.6%) had a CRS (grade 1) event that led to treatment discontinuation. Warnings and recommendations for premedication, monitoring, treatment and dose modifications have been included in the package insert to mitigate the risk of CRS.

ICANS occurred in 10 (6.0%) patients. Most cases (9 out of 10 patients) were grade 1 or 2 in severity. One (0.6%) patient had a fatal ICANS event that was considered related to epcoritamab by the investigator. Except for the fatal event, all other episodes resolved with a median time to resolution of 5.0 days (range: 1, 9). The package insert has included detailed monitoring and management guidelines, including recommended treatment and dose modifications, for managing the risk of ICANS.

Three (1.8%) patients experienced TLS. In 2 (1.2%) patients, the events met the criteria for clinical tumour lysis syndrome (CTLS) (i.e., when laboratory TLS was accompanied by an increased creatinine level, seizures, cardiac dysrhythmia, or death). Both events were grade 3, and in both patients the CTLS events occurred in the setting of disease progression and were unresolved at the time of patient death. The primary cause of death was disease progression for both patients. The package insert has included warnings on TLS as well as recommendations for monitoring and prophylactic treatment for patients at an increased risk for TLS.

TEAEs of infection were reported in 77 (46.1%) patients and serious TEAEs of infection were reported in 27 (16.2%) patients. The most frequently reported serious TEAEs of infection included pneumonia and sepsis in 4 (2.4%) patients each, and COVID-19, COVID-19 pneumonia, and cellulitis in 3 (1.8%) patients each. Serious TEAEs of infection considered to be epcoritamab-related by the investigator included sepsis, upper respiratory tract infection, and oral herpes in 1 (0.6%) patient each. Adequate warnings on infections and recommendations for monitoring and dose modifications have been included in the package insert.

Neutropenia events occurred in 47 (28.1%) patients, with 36 patients experiencing grade 3 or 4 events. Neutropenia was managed with granulocyte-colony stimulating factor (G-CSF) (15.0%) and/or dose delays (4.2%). Febrile neutropenia was reported in 4 (2.4%) patients (3 had grade 3 events and 1 had a grade 4 event). All events resolved with G-CSF treatment. The package insert has included warnings on neutropenia and febrile neutropenia, with recommendations for monitoring, dose modification and management of neutropenia.

Overall, the safety profile of epcoritamab was consistent with that of a bispecific CD3/CD20-directed T-cell engager, with significant toxicities such as CRS, ICANS, TLS and infections. These risks require mitigation measures including premedication, dose modifications, monitoring, and supportive care, which have been described in detail in the package insert.

The safety profile of epcoritamab was considered acceptable in the context of the target population with poor prognosis and limited treatment options.

E ASSESSMENT OF BENEFIT-RISK PROFILE

DLBCL is a life-threatening disease with aggressive nature. For patients with R/R DLBCL who have failed at least two prior lines of therapy, the prognosis is poor and treatment options are limited. Treatment options such as polatuzumab vedotin plus bendamustine and rituximab, selinexor, glofitamab and CAR T-cell therapy are available. However, there remains a medical need for new treatment options for patients with R/R DLBCL given the poor survival outcomes and the absence of optimal therapeutic approaches.

The clinical efficacy of epcoritamab was evaluated in a Phase I/II, open-label, single-arm study in patients with R/R B-cell lymphoma who had received at least two prior systemic therapies. In the pivotal aNHL expansion cohort, treatment with epcoritamab resulted in a clinically meaningful ORR of 61.9% (95% CI: 53.3, 70.0) and a CR rate of 38.8% (95% CI: 30.7, 47.5) as assessed by IRC using Lugano criteria in patients with DLBCL (N=139). The responses were reasonably durable with a median DOR of 12.0 months (95% CI: 6.6, NR). The efficacy results were supported by subgroup analyses of ORR and other secondary efficacy endpoints. The time-to-event endpoints such as PFS and OS were reported but could not be meaningfully interpreted due to the absence of a comparator arm.

The safety profile of epcoritamab was consistent with that expected for a bispecific CD3/CD20-directed T-cell engager. The most notable safety concerns with epcoritamab were CRS, ICANS, TLS and infections. Given the observed toxicities, warnings and recommendations for premedication, dose delays, monitoring, and supportive care have been included in the package insert as risk mitigation measures.

Overall, notwithstanding the lack of a comparator arm in the pivotal study, the magnitude of ORR and CR rate observed with epcoritamab in the DLBCL population was substantial compared with current available therapies, and the safety profile was considered acceptable for the target patient population with poor prognosis and limited treatment options. Therefore, the benefit-risk profile of epcoritamab for the treatment of adult patients with R/R DLBCL after two or more lines of systemic therapy was considered favourable.

F CONCLUSION

Based on the review of quality, safety and efficacy data, the benefit-risk balance of Epkinly for the treatment of adult patients with R/R DLBCL after two or more lines of systemic therapy was deemed favourable and approval of the product registration was granted on 02 October 2024. The approval of this application is subject to conditions requiring the submission of the final study reports of the Phase I/II study GCT3013-01 and Phase III study GCT3013-05.

APPROVED PACKAGE INSERT AT REGISTRATION

EPKINLY CONCENTRATE FOR SOLUTION FOR INJECTION 4 MG/0.8 ML
EPKINLY SOLUTION FOR INJECTION 48 MG/0.8 ML

Epcoritamab

1. PRODUCT NAME

1.1 Generic name
Epcoritamab

1.2 Tradename
EPKINLY

2. INDICATION

EPKINLY 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.

3. DOSAGE AND ADMINISTRATION

3.1 Recommended dosage and premedications

Epcoritamab is for subcutaneous (SC) injection only. Epcoritamab should be administered by a licensed healthcare professional.

Administered epcoritamab according to the following schedule in 28-day cycles.

Table 1: Dosing Schedule

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.			

Administer epcoritamab until disease progression or unacceptable toxicity.

Premedications and Prophylaxis

Epcoritamab should be administered to adequately hydrated patients.

Details on recommended premedication for CRS is shown in Table 2.

Table 2: Epcoritamab Premedications

Cycle	Patient requiring premedication	Premedication	Administration
Cycle 1	All patients	Prednisolone (100 mg oral or IV) or equivalent	• 30-120 minutes prior to each weekly administration of epcoritamab • And for three consecutive days following each weekly administration of EPKINLY in Cycle 1
		• Diphenhydramine (50 mg oral or IV) or equivalent • Acetaminophen (650 to 1,000 mg oral)	• 30-120 minutes prior to the administration of epcoritamab
Cycle 2 and beyond	Patients who experienced Grade 2 or 3[a] CRS with previous dose	• Prednisolone (100 mg oral or IV) or equivalent	• 30-120 minutes prior to next administration of EPKINLY after a grade 2 or 3[a] CRS event • And for three consecutive days following the next administration of EPKINLY until EPKINLY is given without subsequent CRS of Grade 2 or higher
[a] Patients will be permanently discontinued from EPKINLY after a Grade 4 CRS event.			

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

Monitor patients for potential CRS and immune effector cell-associated neurotoxicity syndrome (ICANS) following EPKINLY administrations during Cycle 1 and in subsequent cycles as needed at the physician's discretion. Following administration of the first full dose, patients should remain within close proximity to a healthcare facility that can assess and manage potential CRS and /or ICANS for at least 24 hours. Counsel patients 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 **Warnings and Precautions (5.1 and 5.2)**).

3.2 Missed or Delayed Dose

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).

3.3 Dosage Modifications and Management of Adverse Reactions

Cytokine Release Syndrome (CRS)

Patients treated with EPKINLY 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 3. Patients who experience CRS should be monitored more frequently during next scheduled EPKINLY administrations.

Table 3: CRS Grading and Management Guidance

Grade[1]	**Recommended Therapy**	**EPKINLY Dose Modification**
Grade 1 • Fever (temperature ≥ 38°C) without hypotension or hypoxia	**Anti-cytokine Therapy:** Consider anti-cytokine therapy in certain cases, e.g., advanced age, high tumor burden, circulating tumor 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 (e.g., siltuximab, anakinra). See **Table 4.** **Corticosteroids** In case of concurrent ICANS, initiation of corticosteroids are highly recommended. Consider Dexamethasone 10-20 mg per day (or equivalent).	Hold EPKINLY until resolution of CRS event.

Grade[1]	Recommended Therapy	EPKINLY Dose Modification
Grade 2[a] • Fever (temperature ≥ 38°C) **AND** • Hypotension not requiring vasopressors. **AND/OR** • Hypoxia requiring low-flow (≤6 L/minute) nasal cannula or blow-by	**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 (e.g., siltuximab, anakinra) See **Table 4.** **Corticosteroids:** In case of concurrent ICANS, initiation of corticosteroids is highly recommended. Consider dexamethasone 10-20 mg per day (or equivalent).	Hold EPKINLY until resolution of CRS event.
Grade 3[a] • Fever (temperature ≥ 38°C) **AND** • 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	**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 (e.g., siltuximab, anakinra) See **Table 4.**	Hold EPKINLY until resolution of CRS event.

Grade[1]	Recommended Therapy	EPKINLY Dose Modification
	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** Hypotension requiring ≥ 2 vasopressors (excluding vasopressin) **AND/OR** • Hypoxia requiring positive pressure ventilation (e.g. CPAP, BiPAP, intubation and mechanical ventilation)	**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 (e.g., siltuximab, anakinra) See **Table 4.** **Corticosteroids** Dexamethasone (e.g., 10-20 mg IV every 6 hours). If no response, initiate methylprednisolone 1000 mg/day.	Permanently discontinue EPKINLY
[1] CRS graded according to ASTCT 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 EPKINLY 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 4.

Table 4: ICANS Grading and Management Guidance

Grade[a]	Recommended Therapy	EPKINLY Dose Modification
Grade 1 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 <u>Anti-cytokine therapy</u> *No concurrent CRS*: Anti-cytokine therapy not recommended. *Concurrent CRS*: Anti-cytokine therapy recommended. Choose alternative to tocilizumab (e.g., siltuximab, anakinra) if possible. • Consider anakinra as a daily dose of 100 mg SC or 200 mg SC (100 mg every 12 hours) depending on the severity of neurotoxicity and other concurrent toxicities. Anakinra should be given until resolution of neurotoxicity and other concurrent toxicities which could benefit from anakinra treatment. • Consider siltuximab, 11 mg/kg IV over 1 hour, one time only.	Hold EPKINLY until resolution of event.
Grade 2 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. <u>Anti-cytokine therapy:</u> *No concurrent CRS:* Anti-cytokine therapy not recommended. *Concurrent CRS:* Anti-cytokine therapy recommended. Choose alternative to tocilizumab (e.g., siltuximab, anakinra) if possible. • Consider anakinra as a daily dose of 100 mg SC or 200 mg SC (100 mg every 12 hours) depending on the severity of neurotoxicity and other concurrent toxicities. Anakinra should be given until resolution of neurotoxicity and other	Hold EPKINLY until resolution of event.

Grade[a]	Recommended Therapy	EPKINLY Dose Modification
	concurrent toxicities which could benefit from anakinra treatment. • Consider siltuximab, 11 mg/kg IV over 1 hour, one time only.	
Grade 3 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]	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. <u>Anti-cytokine Therapy</u> *No concurrent CRS:* Anti-cytokine therapy not recommended. *Concurrent CRS:* Anti-cytokine therapy recommended: Choose alternative to tocilizumab (e.g., siltuximab, anakinra) if possible. • Consider anakinra as a daily dose of 100 mg SC or 200 mg SC (100 mg every 12 hours) depending on the severity of neurotoxicity and other concurrent toxicities. Anakinra should be given until resolution of neurotoxicity and other concurrent toxicities which could benefit from anakinra treatment. • Consider siltuximab, 11 mg/kg IV over 1 hour, one time only.	**First episode:** delay EPKINLY until full resolution of event. **Second episode:** permanently discontinue EPKINLY.
Grade 4 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	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. <u>Anti-cytokine therapy</u>: *No concurrent CRS:* Anti-cytokine therapy not recommended.	Permanently discontinue EPKINLY.

Grade[a]	Recommended Therapy	EPKINLY Dose Modification
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: o diffuse cerebral oedema on neuroimaging, or o decerebrate or decorticate posturing, or o cranial nerve VI palsy, or o papilloedema, or o Cushing's triad	*Concurrent CRS:* Anti-cytokine therapy recommended. Choose alternative to tocilizumab (e.g., siltuximab, anakinra) if possible. • Consider anakinra as a daily dose of 100 mg SC or 200 mg SC (100 mg every 12 hours) depending on the severity of neurotoxicity and other concurrent toxicities. Anakinra should be given until resolution of neurotoxicity and other concurrent toxicities which could benefit from anakinra treatment. • Consider siltuximab, 11 mg/kg IV over 1 hour, one time only.	

[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 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

Table 5: Recommended Dosage Modifications for Other Adverse Reactions

Adverse Reaction[1]	Severity[1]	Action
Infections	Grades 1-4	Withhold EPKINLY in patients with active infection, until the infection resolves For Grade 4, consider permanent discontinuation of EPKINLY
Neutropenia or febrile neutropenia	Absolute neutrophil count less than 0.5×10^9/L	Withhold EPKINLY until absolute neutrophil count is 0.5×10^9/L or higher
Thrombocytopenia	Platelet count less than 50×10^9/L	Withhold EPKINLY until platelet count is 50×10^9/L or higher
Other Adverse Reactions	Grade 3 or higher	Withhold EPKINLY 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.		

3.4 Preparation and Administration

Epcoritamab should be prepared and administered by a healthcare provider as subcutaneous injection (SC). Each vial of epcoritamab is intended for single dose only.

The administration of EPKINLY takes place over the course of 28-day cycles, following the dosing scheduled in Section 3.1.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Dose Preparation
Use aseptic technique to prepare EPKINLY. Filtration of the diluted solution is not required.

Preparation instructions for 0.16 mg and 0.8 mg doses of EPKINLY

0.16 mg Priming Dose Preparation Instructions – *(2 dilutions required)*
Use an appropriately sized syringe, vial, and needle for each transfer step.

1) Prepare EPKINLY vial a) Retrieve one 4 mg/0.8 mL EPKINLY vial from the refrigerator. b) Allow the vial to come to room temperature for no more than 1 hour c) Gently swirl the EPKINLY vial. **DO NOT** invert, 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 EPKINLY** into the **Dilution A** vial. c) Transfer **4.2 mL of 0.9% Sodium Chloride Injection, sterile solution,** into the **Dilution A** vial. 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** into the **Dilution B** vial. The **Dilution A** vial is no longer needed. c) Transfer **8 mL of 0.9% Sodium Chloride Injection, 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 a) Withdraw **1 mL of the diluted epcoritamab** from the **Dilution B** vial into a syringe.
5) Label syringe Label the syringe with the dose strength (0.16 mg) and the time of day.

Discard the vial and any unused portion of EPKINLY in accordance with local requirements.

0.8 mg Intermediate Dose Preparation Instructions – ***(1 dilution required)***
Use an appropriately sized syringe, vial, and needle for each transfer step.

1) Prepare EPKINLY vial a) Retrieve one 4 mg/0.8 mL EPKINLY vial from the refrigerator. b) Allow the vial to come to room temperature for no more than 1 hour. c) Gently swirl the EPKINLY vial. **DO NOT** invert, 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 EPKINLY** into the **Dilution A** vial. c) Transfer **4.2 mL of 0.9% Sodium Chloride Injection, 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 a) Withdraw **1 mL of the** diluted epcoritamab from the **Dilution A** vial into a syringe.
4) Label syringe Label the syringe with the dose strength (0.8 mg) and the time of day.

Discard the vial and any unused portion of EPKINLY in accordance with local requirements.

48 mg Full Dose Preparation Instructions *(No dilution required)*
EPKINLY 48mg/0.8mL vial is supplied as ready-to-use solution that does not need dilution prior to administration.

1) Prepare EPKINLY vial a) Retrieve one 48 mg/0.8 mL EPKINLY vial from the refrigerator. b) Allow the vial to come to room temperature for no more than 1 hour.

c) Gently swirl the EPKINLY vial. **DO NOT** invert, vortex, or vigorously shake the vial.
2) Withdraw dose Withdraw **0.8 mL of the EPKINLY** into a syringe.
3) Label syringe Label the syringe with the dose strength (48 mg) and the time of day.

Discard the vial and any unused portion of EPKINLY in accordance with local requirements.

Storage for Diluted and Prepared EPKINLY
Use immediately or store EPKINLY solution in a refrigerator and protect from light up to 24 hours at 2°C to 8 °C (36 F° to 46F°) from the time of preparation. Within these 24 hours, the EPKINLY solution can be stored for 12 hours at room temperature from the start of dose preparation to administration. Minimize exposure to daylight. Allow EPKINLY solution to equilibrate to room temperature before administration. Discard unused EPKINLY solution beyond the allowable storage time.

Site Administration
The injection site should be preferably in the lower part of abdomen or the thigh. Change of injection site from left or right side or vice versa is recommended especially during the weekly administration (Cycles 1-3).

3.5 Dosing in Special Populations

3.5.1 Pediatrics
The safety and efficacy of epcoritamab in children aged less than 18 years of age have not yet been established.

3.5.2 Geriatric
In patients with LBCL in EPCORE NHL-1, 48 (31%) were ≥65 to <75 years of age and 29 (18%) were ≥75 years of age. No clinically meaningful differences in safety or efficacy were observed between patients ≥65 years of age compared with younger adult patients.

3.5.3 Renal impairment
Dose adjustments are not considered necessary in patients with mild to moderate renal impairment. No dose recommendations can be made for patients with severe renal impairment to end-stage renal disease.

3.5.4 Hepatic impairment
Dose adjustments are not considered necessary in patients with mild hepatic impairment. No dose recommendations can be made for patients with moderate to severe hepatic impairment.

4. CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients listed in section 15.2

5. WARNINGS AND PRECAUTIONS

5.1 Cytokine Release Syndrome

Cytokine Release Syndrome, 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 greater than two patients include chills, tachycardia, headache and dyspnea.

The median time to onset of CRS from the most recent administered epcoritamab dose was 2 days (range: 1 to 11 days). The median time to onset after the first full dose was 20.6 hours (range: 0.2 days to 7 days). Most CRS events occurred in Cycle 1 and were associated with the first full dose of epcoritamab. The median duration of CRS was 2 days (range: 1 to 27 days). Administer prophylactic corticosteroids to mitigate the risk of CRS [see **Dosage and Administration** (**3.1**)].

Monitor patients for potential CRS following epcoritamab administrations during Cycle 1 and in subsequent cycles as needed at the physician's discretion. Following administration of the first full dose, patients should remain within close proximity to a healthcare facility that can assess and manage potential CRS for at least 24 hours. At the first signs or symptoms of CRS, institute treatment of supportive care with tocilizumab and/or corticosteroids as appropriate. 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 **Dosage and Administration (3.1, 3.3)**].

5.2 Immune Effector Cell Associated Neurotoxicity Syndrome (ICANS)

ICANS, including a fatal event, have occurred in patients receiving epcoritamab. ICANS may manifest as aphasia, altered level of consciousness, impairment of cognitive skills, motor weakness, seizures, and cerebral edema.

The median time to onset of ICANS from the start of epcoritamab treatment (Cycle 1 Day 1) was 16.5 days (range: 8 to 141 days). The majority of cases of ICANS occurred within the Cycle 1 of epcoritamab treatment, however some occurred with delayed onset. The median duration of ICANS was 5 days (range: 1, 9 days). The onset of ICANS can be concurrent with CRS, following resolution of CRS or in the absence of CRS.

Monitor patients for signs and symptoms of ICANS following epcoritamab administrations during Cycle 1 and in subsequent cycles as needed at the physician's discretion. Following administration of the first full dose, patients should remain within close proximity to a healthcare facility that can assess and manage potential ICANS for at least 24 hours. At the first signs or symptoms of ICANS institute treatment with corticosteroids and non-sedating-anti-seizure medications as appropriate. (See **Dosage and Administration** (**3.3**)). 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 [**Dosage and Administration** (**3.1, 3.3**)].

5.3 Serious Infections

Treatment with EPKINLY may lead to an increased risk of infections. Serious infections, including fatal infections were observed in patients treated with EPKINLY in clinical trials [**Adverse Reactions** (9.3)].

Avoid administration of EPKINLY in patients with clinically significant active systemic infections. As appropriate, administer prophylactic antimicrobials **[Dosage and Administration (3.1)**]. Monitor patients for signs and symptoms of infections prior to and during treatment and treat according to standard/local guidelines and practice. 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.

5.4 Immunization

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

5.5 Tumour lysis syndrome (TLS)

TLS has been reported in patients receiving EPKINLY [see **Adverse Reactions (9.1)**]. 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.

5.6 CD20-negative disease

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

6. DRUG INTERACTIONS

No formal drug interaction studies have been conducted with EPKINLY.

Transient elevation of certain proinflammatory cytokines by EPKINLY may suppress CYP450 enzyme activities. On initiation of EPKINLY therapy in patients being treated with CYP450 substrates with a narrow therapeutic index, therapeutic monitoring should be considered.

7. PREGNANCY AND LACTATION

7.1 Pregnancy

Based on its mechanism of action, EPKINLY may cause fetal harm, including B-cell lymphocytopenia and alterations in normal immune responses, when administered to pregnant women. There are no data on the use of EPKINLY in pregnant women. Animal reproduction studies have not been conducted

with EPKINLY. IgG1 antibodies, such as EPKINLY, can cross the placenta resulting in fetal exposure. Advise pregnant women of the potential risk to a fetus. EPKINLY is not recommended during pregnancy and in women of childbearing potential not using contraception.

7.1.1 Data (animal and/or human)
Animal reproduction studies have not been conducted with EPKINLY. There are no data on the use of EPKINLY in pregnant women.

7.2 Lactation

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

7.3 Females and Males of Reproductive Potential

7.3.1 Reproduction
Verify pregnancy status in females of reproductive potential prior to initiating EPKINLY treatment.

7.3.2 Contraception
Females of reproductive potential should use effective contraception during treatment with EPKINLY and for at least 4 months after the last dose.

7.3.3 Fertility (males)
No fertility studies have been conducted with EPKINLY (see **PRE-CLINICAL SAFETY DATA (14)**). The effect of EPKINLY on male and female fertility is unknown.

8. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No formal studies on the effect of EPKINLY on the ability to drive and operate machines have been performed. Due to the potential for ICANS, patients should be advised to exercise caution while (or avoid if symptomatic) driving or using heavy or potentially dangerous machines.

9. ADVERSE REACTIONS

9.1 Clinical trials experience

EPCORE™ NHL-1

The safety of EPKINLY was evaluated in a non-randomized, single-arm study in 167 patients with relapsed or refractory LBCL after two or more lines of systemic therapy and included all patients who enrolled to the 48 mg dose and received at least one dose of EPKINLY.

The median duration of exposure to EPKINLY was 3.7 months (range: 0 to 20 months).

Serious adverse reactions occurred in 40% of patients; the most frequent serious adverse reaction (≥ 10%) was cytokine release syndrome (31%). Two patients (1.2%) experienced a fatal adverse reaction; one each for ICANS and pneumonia.

Discontinuation due to adverse reactions occurred in 2.4% of patients. Discontinuation of epcoritamab due to pneumonia occurred in 2 patients and discontinuation due to CRS or ICANS occurred in 1 patient (each).

Dose delays due to adverse reactions occurred in 20% of patients. Adverse reactions leading to dose delays (≥3%) were CRS (7.2%), neutropenia (4.2%), pyrexia (3.0%), and thrombocytopenia (3.0%).

Table 6 provides adverse reactions reported in patients with relapsed or refractory LBCL. Adverse reactions are listed by MedDRA body system organ class, rate, and frequency.
Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000), not known (cannot be estimated from available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 6: Adverse Reactions Reported in Patients with Relapsed or Refractory LBCL treated with Epcoritamab in EPCORE NHL-1 Study

Adverse Reaction by Body System	**Epcoritamab N=167**		
	All Grades Frequency	All Grades (%)	Grade ≥3 (%)
Infections and infestations			
Pneumonia[a]	Common	7.2	3.6
Upper respiratory tract infection[b]	Common	6.0	1.2
Neoplasm benign, malignant and unspecified (including cysts and polyps)			
Tumour flare	Common	3.0	
Blood and lymphatic system disorders			
Neutropenia[c]	Very common	28	22
Anemia[d]	Very common	19	10
Thrombocytopenia[e]	Very common	15	7.2
Febrile Neutropenia	Common	2.4	2.4
Immune system disorders			
Cytokine release syndrome[f]	Very common	50	2.4
Metabolism and nutrition disorders			
Tumor lysis syndrome[g]	Common	1.8	1.8
Nervous system disorders			
Headache	Very common	13	0.6

Adverse Reaction by Body System	**Epcoritamab N=167**		
	All Grades Frequency	All Grades (%)	Grade ≥3 (%)
Immune effector cell-associated neurotoxicity syndrome[f]	Common	6.0	0.6
Gastrointestinal disorders			
Nausea	Very Common	20	1.2
Diarrhea	Very Common	20	
Vomiting	Very Common	12	0.6
Skin and subcutaneous tissue disorders			
Rash[h]	Common	7.8	
Pruritus	Common	6.6	
General disorders and administration site conditions			
Injection site reactions[i]	Very Common	30	
Pyrexia[j]	Very Common	23	

Events were graded using NCI CTCAE version 5.0.
CRS events were graded using ASTCT consensus criteria (Lee et. al., 2019)
[a] Pneumonia includes COVID-19 pneumonia and pneumonia.
[b] Upper respiratory tract infection includes laryngitis, pharyngitis, respiratory syncytial virus infection, rhinitis, rhinovirus infection, and upper respiratory tract infection
[c] Neutropenia includes neutropenia and neutrophil count decreased.
[d] Anemia includes anemia and serum ferritin decreased.
[e] Thrombocytopenia includes platelet count decreased and thrombocytopenia.
[f] Events graded using American Society for Transplant and Cellular Therapy consensus criteria
[g] Clinical Tumour Lysis Syndrome was graded based on Cairo-Bishop.
[h] Rash includes rash, rash erythematous, rash maculo-papular, and rash pustular.
[i] Injection site reactions include injection site bruising, injection site erythema, injection site hypertrophy, injection site inflammation, injection site mass, injection site pain, injection site pruritus, injection site rash, injection site reaction, injection site swelling, and injection site urticaria.
[j] Pyrexia includes pyrexia and body temperature increased.

9.2 Post marketing experience

- N/A

9.3 Important Adverse Reactions

Cytokine Release Syndrome

CRS of any grade occurred in 50% (84/167) of patients treated with EPKINLY. The incidence of Grade 1 was 31% (52/167), Grade 2 was 17% (28/167), and Grade 3 was 2.4% (4/167). The median time to

onset of CRS from the most recent administered EPKINLY dose was 2 days (range: 1 to 11 days). CRS resolved in 98.8% of patients, and the median duration of CRS events was 2 days (range 1-27 days).

The most common signs and symptoms of CRS included pyrexia 50% (83/167), hypotension 16% (26/167) and hypoxia 9.6% (16/167). Other signs and symptoms of CRS in greater than two patients included chills (4.8%), tachycardia (including sinus tachycardia [7.8%]), headache (13%) and dyspnea (7.8%). In addition to corticosteroids use, tocilizumab was used to manage CRS event in 15% of patients.

Immune Effector Cell Associated Neurotoxicity Syndrome (ICANS)

ICANS occurred in 6% of patients treated with EPKINLY; 4.2% experienced Grade 1 and 1.2% experienced Grade 2. One patient (0.6%) experienced an ICANS event of Grade 5 (fatal). The median time to first ICANS onset from the start of EPKINLY treatment was 16.5 days (range: 8 to 141 days). ICANS resolved in 90% (9/10) of patients with supportive care. The median time to resolution of ICANS was 5 days (range: 1 to 9 days).

Serious Infections

Serious infections occurred in 16% of patients treated with EPKINLY. The most frequent serious infections were pneumonia (2.4%), sepsis (2.4%), COVID-19 (1.8%), COVID-19 pneumonia (1.8%), bacteremia (1.2%), septic shock (1.2%), and upper respiratory tract infection (1.2%). Fatal serious infections occurred in 4 (2.4%) patients.

Immunogenicity

Epcoritamab has the potential to induce anti-drug-antibodies (ADA). The incidence of antibodies to epcoritamab was low and all the patients who were positive had low titers (≥1 in 0.6% (1/158)). Due to the low number of patients with ADAs, a meaningful analysis of the impact of ADAs on safety is limited (see **Pharmacokinetics in special populations (12.4)**).

Laboratory Abnormalities

Grade 3 or 4 laboratory abnormalities worsening from baseline reported in at least 10% of patients with LBCL within the EPCORE NHL-1 study were lymphocyte count decreased (78%), neutrophil count decreased (31%), hemoglobin decreased (13%), and platelets decreased (13%).

10. DRUG ABUSE AND DEPENDENCY

N/A

11. OVERDOSE

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

12. PHARMACOLOGIC PROPERTIES

12.1 Mechanism of action

Epcoritamab is a humanized 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 leukemias 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).

12.2 Pharmacodynamics

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.

Following subcutaneous administration of epcoritamab, 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.

12.3 Pharmacokinetics

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 characterized by inter-individual variability (IIV) ranging from 25.7% to 137.5% coefficient of variation (CV) for epcoritamab PK parameters.

Following the recommended 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.

12.3.1 Absorption

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

12.3.2 Distribution
The geometric mean (% CV) central volume of distribution is 8.27 L (27.5%) based on population PK modeling.

12.3.3 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.

12.3.4 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.

12.4 Pharmacokinetics in 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 <30ml/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). Therefore, the pharmacokinetics of epcoritamab is unknown in these populations.
Like other therapeutic proteins, body weight (39 to 144 kg) has a statistically significant effect on the pharmacokinetics of epcoritamab, however this effect is not clinically relevant across body weight categories (<65kg, 65-<85, ≥85).

12.4.1 Pediatric
The pharmacokinetics of epcoritamab in pediatric patients has not been established.

12.4.2 Immunogenicity

In EPCORE clinical study, 4 of 158 (2.5%) patients who were treated with EPKINLY at the full dose of 48 mg and evaluable for the presence of anti-drug antibodies (ADA) tested positive for anti-epcoritamab antibodies on treatment (two at cycle 2 day 22, one at cycle 1 day 22, and one at cycle 2 day 1) with titers of 1:320 or less. There was no evidence of an altered pharmacokinetic profile with anti-epcoritamab binding antibody development based on a population PK analysis. There are insufficient data to evaluate the effect of ADA on the safety or efficacy of epcoritamab.

12.5 Drug interactions

No formal drug-drug interaction studies have been performed.

13. CLINICAL STUDIES

EPCORE NHL-1

Study EPCORE NHL-1 was an open-label, multi-cohort, multicenter, 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, 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).

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, had lymphocyte counts < 5×10^9/L, and received at least 1 prior anti-CD20 monoclonal antibody-containing therapy.

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 139 patients with DLBCL who had received EPKINLY subcutaneously (SC) in cycles of 4 weeks, i.e., 28 days. Epcoritamab was administered as a monotherapy as follows:

- Cycle 1: EPKINLY 0.16 mg on Day 1, 0.8 mg on Day 8, 48 mg on Day 15 and Day 22
- Cycles 2-3: EPKINLY 48 mg on Days 1, 8, 15, and 22
- Cycles 4-9: EPKINLY 48 mg on Days 1 and 15
- Cycles 10 and beyond: EPKINLY 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 7.

Table 7: 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, (%)	61
Race	
White; %	60
Black, or African American; %	0
Asian; %	19
Other; %	4
Not Reported; %	17
ECOG performance status; %	
0	48
1	48
2	4
Number of Prior Lines of anti-lymphoma therapy, %	
Median (min, max)	3 (2, 11)
2	30
3	34
≥4	37
Disease Type at Study Entry; (%)	
DLBCL	100
DLBCL Disease history; %	
De Novo DLBCL	70
DLBCL transformed from indolent lymphoma	29
FISH Analysis Per Centra Lab, N=88	
Double-hit/Triple-hit lymphoma, (%)	14
Prior Therapy; (%)	
Prior CAR-T	38
Prior autologous HSCT	19
Primary refractory disease[a]	59
Refractory to ≥ 2 consecutive lines of prior anti-lymphoma therapy[b]	75
Refractory to the last line of systemic antineoplastic therapy[b]	82
Refractory to anti-CD20 therapy in last line	84
Refractory to CAR-T	28
PoliVy	9
Topoisomerase inhibitor	67

[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 10.7 months (range: 0.3 to 17.9 months).

Table 8: Efficacy Results in Study EPCORE NHL-1 in DLBCL Patients

Endpoint [a] **IRC assessment**	**Epcoritamab** **(N=139)**
ORR , n (%)	86 (62)
(95% CI)	(53.3, 70)
CR, n (%)	54 (39)
(95% CI)	(30.7, 47.5)
PR, n (%)	32 (23)
(95% CI)	(16.3, 30.9)
DOR	
Median (95% CI), months	12 (6.6, NR)
6-month estimate, % (95% CI)	63 (51.5, 73)
9-month estimate, % (95% CI)	62 (49.7, 71.5)
DOCR	
Median (95% CI), months	12 (9.7, NR)
6-month estimate, % (95% CI)	85 (70, 93.2)
9-month estimate, % (95% CI)	85 (70, 93.2)
DOR if Best Response is CR	
Median (95% CI), months	NR (12, NR)
6-month estimate, % (95% CI)	88 (74.6, 94.3)
9-month estimate, % (95% CI)	88 (74.6, 94.3)
PFS	
Median (95% CI), months	4 (3, 8.2)
6-month estimate % remaining in PFS, (95% CI)	44 (35.4, 52.4)
9-month estimate % remaining in PFS, (95% CI)	40 (31.2, 48.4)
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; PFS = progression-free survival; TTR = time to response

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

The median time to CR was 2.7 months (range: 1.2 to 11.1 months).

Response durations were longer in patients who achieved CR, as compared to patients with a best response of partial response (PR) (Table 8).

The overall response rates and complete response rates with EPKINLY were consistent across the following subgroups: age, number of or response to prior lines of therapy, and prior CAR-T experience.

In subgroup analysis of patients (n = 53) who received CAR-T, the ORR was 53% (95% CI: 39, 67), and the CR rate was 34% (95% CI: 22, 48). Median duration of response for these patients was 9.7 months (95% CI: 5.4, NR), and the median progression-free survival was 2.7 months (95% CI: 1.4, 11).

In subgroup analysis of patients (n = 86) with no prior CAR-T, the ORR was 67% (95% CI: 56, 77), and the CR rate was 42% (95% CI: 31, 53). Median duration of response for these patients was 12 months (95% CI: 5.6, NR); and the median progression-free survival was 5.4 months (95% CI: 3.7, NR).

In a pre-specified subgroup analysis of patients (n = 82) who were primary refractory to anti-lymphoma therapy, the ORR was 54% (95% CI: 42, 65), and the CR rate was 30% (95% CI: 21, 42).
Median overall survival (OS) for patient on EPKINLY was not reached.

Key patient reported outcomes (PROs) were captured by the FACT-Lym to assess the impact of EPKINLY on patient quality of life. The FACT-Lym is a fully validated questionnaire to assess the quality-of-life patients with lymphoma. It consists of a general quality of life instrument (FACT-G) and a condition specific module, Lym. The FACT-G covers 5 subscales (Physical Well-Being, Social/Family Well-Being, Emotional Well-Being, Functional Well-Being, and Additional Concerns). The Lym module consists of 15 statements patients need to endorse on an identical 5-point scale. The Trial Outcome Index (TOI) is a subscore consisting of the Physical Well-Being, Functional Well-Being and Lym subscales (LymS).

Six questions from the FACT Lym addresses six key lymphoma symptoms (body pain, fever, night sweats, lack of energy, tires easily, and weight loss), as well as FACT-LymS and FACT-TOI. While on treatment, there were improvements in the patient reported symptoms across all six key lymphoma symptoms from C2D1 to C13D1. Steady and consistent improvements in FACT-LymS and FACT-TOI were also observed while patients were on treatment.

Mean (Standard Deviation) scores from C2D1 to C13D1 are as follows: Body pain: 1.3 (1.25) to 0.4 (0.6); Fever: 0.4 (0.85) to 0.0 (0.00); Night sweats: 0.5 (0.80) to 0.2 (0.42); Lack of energy: 1.8 (1.12) to 0.6 (0.61); Tires easily: 1.8 (1.11) to 0.9 (0.66); Weight loss: 0.8 (0.93) to 0.1 (0.32).

Mean (standard deviation) FACT-LymS scores improved from 42.4 (10) at baseline (C1D1, N=122) to 51.1 (6.36) at C9D1 (N=43), the final on-treatment time point measured. The mean (standard deviation) change in FACT-LymS scores from baseline consistently increased from 3.6 (6.98) by C3D1 to 5.7 (7.73) at C9D1.

Mean (standard deviation) FACT-TOI scores improved from 79.7 (20.03) at baseline (C1D1, N=122) to 94.2 (13.06) at C9D1 (N=43), the final on-treatment time point measured. The magnitude of improvement was reflected in the mean (standard deviation) change in TOI scores from baseline ranging from 5.0 (12.26) by C3D1 to 8.5 (15.52) at C9D1.

The PRO results should be interpreted with caution in the context of the open-label and single-arm study design.

In patients with HGBCL including HGBCL NOS (N=9) and HGBCL with MYC and BCL2 and/or BCL6 rearrangements (DLBCL DH/TH; N=12) using central FISH analysis, the ORR was 47.6% (95% CI: 25.7, 70.2) and CR rate was 28.6% (95% CI: 11.3, 52.2). Patients with HGBCL had a median DOR of 12.0 months (95% CI: 1.1, NR) and a median DOCR of 12.0 months (95% CI, NR, NR).

14. PRE-CLINICAL SAFETY DATA

14.1 Carcinogenicity

Carcinogenicity studies have not been conducted with epcoritamab.

14.2 Mutagenicity

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

14.3 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.

14.4 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.

15. PHARMACEUTICAL PROPERTIES

15.1 Description

Epcoritamab is a humanized bispecific antibody that specifically binds to CD3+ T-cells and CD20+ B cells. Epcoritamab is manufactured from two biological intermediates, which are produced in Chinese hamster ovary (CHO) cells using recombinant DNA technology and has an approximate molecular weight of 149 kDa.

Epcoritamab has a regular IgG1 structure and biochemical characteristics typical of human IgG1.

Each single-dose 4 mg vial contains 4 mg of epcoritamab, 2.82 mg of sodium acetate trihydrate, 0.19 mg of acetic acid, 21.9 mg of D-sorbitol, 0.32 mg of polysorbate 80, and water for injection, adjusted to a pH of 5.5.

Each single-dose 48 mg vial contains 48 mg of epcoritamab, 2.82 mg of sodium acetate trihydrate, 0.19 mg of acetic acid, 21.9 mg of D-sorbitol, 0.32 mg of polysorbate 80, and water for injection, adjusted to a pH of 5.5.

15.2 List of excipients

Sodium acetate trihydrate
Acetic acid
D-sorbitol
Polysorbate 80
Water for injection

15.3 Instruction for preparation

See Section 3.4

15.4 Storage

Store and transport refrigerated (2°C - 8°C).

Keep in the original carton to protect from light. Do not freeze. Do not shake.

15.5 How Supplied

Epcoritamab concentrate for solution, for subcutaneous injection (4 mg [5 mg/mL]) or epcoritamab solution for subcutaneous injection (48 mg [60 mg/mL]) is a sterile, preservative free, clear to slightly opalescent, colorless to slightly yellow solution, practically free of visible particles, supplied in glass vials as:

- 4 mg per 0.8 mL single dose vial
- 48 mg per 0.8 mL single dose vial.

Product Registrant:
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