swissmedic

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Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Tepkinly

International non-proprietary name: epcoritamab

Pharmaceutical form: concentrate for solution for injection

Dosage strength(s): 4 mg/0.8 ml

Route(s) of administration: subcutaneous use

Marketing authorisation holder: AbbVie AG

Marketing authorisation no.: 69161

Decision and decision date: temporary authorisation in accordance with Art. 9a TPA approved on 15.02.2024

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

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1 Terms, Definitions, Abbreviations

3L	Third-line therapy
AESI	Adverse event of special interest
ASCT	Autologous stem cell transplantation
B-NHL	B-cell non-Hodgkin lymphoma
CHMP	Committee for Medicinal Products for Human Use
C_{max}	Maximum observed plasma/serum concentration of drug
CRS	Cytokine release syndrome
DLBCL	Diffuse large B-cell lymphoma
DOR	Duration of response
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
HC	Heavy chain
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICANS	Immune effector cell-associated neurotoxicity syndrome
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
LBCL	Large B-cell lymphoma
LoQ	List of Questions
mAb	Monoclonal antibody
MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
N/A	Not applicable
ORR	Objective response rate
OS	Overall survival
PFS	Progression-free survival
RMP	Risk management plan
r/r DLBCL	Recurrent or refractory diffuse large B-cell lymphoma
SAE	Serious adverse event
SC	Subcutaneous use
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

2 Background information on the procedure

2.1 Applicant's request(s)

New active substance status
The applicant requested new active substance status for epcoritamab in the above-mentioned medicinal product.

Orphan drug status
The applicant requested orphan drug status in accordance with Article 4 a^{decies} no. 2 of the TPA.
Orphan drug status was granted on 10 November 2022.

Temporary authorisation for human medicinal products
The applicant requested a temporary authorisation in accordance with Article 9a TPA.

2.2 Indication and dosage

2.2.1 Requested indication

Tepkinly is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after 2 or more lines of systemic therapy, where patient is unable to receive, or has previously received, CAR-T cell therapy.

This indication has been granted temporary authorisation as the clinical data were incomplete at the time the application was assessed (Art. 9a Therapeutic Products Act). The temporary authorisation is contingent on the timely fulfilment of conditions. After they have been met, the temporary authorisation can be converted into an ordinary authorisation.

2.2.2 Approved indication

Tepkinly is indicated as monotherapy for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), after 2 or more lines of systemic therapy, including a CD20 antibody, where patient is unable to receive, or has previously received, anti-CD19-targeted CAR-T cell therapy (see "Clinical efficacy" section).

This indication has been granted temporary authorisation as the clinical data were incomplete at the time the application was assessed (Art. 9a Therapeutic Products Act). The temporary authorisation is contingent on the timely fulfilment of conditions. After they have been met, the temporary authorisation can be converted into an ordinary authorisation.

2.2.3 Requested dosage

Summary of the requested standard dosage:
The requested dosing regimen includes an initial priming dose of 0.16 mg (C1D1), an intermediate dose of 0.8 mg (C1D8), and a full dose of 48 mg epcoritamab at C1D15, C1D22, and thereafter administered subcutaneously in cycles of 28 days according to the following schedule:

- Cycles 1 to 3: once weekly (QW) on Days 1, 8, 15, and 22
- Cycles 4 to 9: once every 2 weeks (Q2W) on Days 1 and 15
- Cycle 10 and beyond until unacceptable toxicity or progressive disease: once every 4 weeks (Q4W) on Day 1.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	6 July 2023
Formal control completed	7 July 2023
List of Questions (LoQ)	1 September 2023
Response to LoQ	24 October 2023
Preliminary decision	8 December 2023
Response to preliminary decision	22 January 2024
Final decision	15 February 2024
Decision	approval (temporary authorisation in accordance with Art. 9a TPA)

3 Medical context

Diffuse large B-cell lymphoma (DLBCL) is the most frequent aggressive B-cell non-Hodgkin lymphoma, with an incidence of roughly 4/100,000/year in Europe and a higher incidence in men than in women[1].

The intent of treatment is curative in first-line therapy and, in many cases, in later lines of therapy as well. First-line therapy consists of poly immune-chemotherapy and is curative in many cases. The prognosis is worse for patients with primary refractory disease or early recurrent disease. There are various treatment options for later lines of therapy, all of them with relevant toxicity and limited efficacy[2]. The main differentiation in the treatment of recurrent or refractory DLBCL (r/r DLBCL) is between patients who are eligible for high-dose chemotherapy with subsequent autologous stem cell transplantation (ASCT) and those who are not.

Various therapeutic options exist for r/r DLBCL patients who are not eligible for ASCT. These comprise different immune-chemotherapy regimens, combinations of immunochemotherapy with antibody-drug conjugates, and the chemotherapy-free therapeutic option of a CD19 antibody in combination with an immunomodulator. For third-line treatment of r/r DLBCL, the currently preferred treatment for eligible patients is CAR T-cell therapy, if this has not been used in earlier treatment lines.

[1] Tilly H, Gomes da Silva M, Vitolo U, Jack A, Meignan M, Lopez-Guillermo A, Walewski J, André M, Johnson PW, Pfreundschuh M, Ladetto M; ESMO Guidelines Committee. Diffuse large B-cell lymphoma (DLBCL): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2015 Sep;26 Suppl 5:v116-25. doi: 10.1093/annonc/mdv304. PMID: 26314773.

[2] Georg Lenz, Björn Chapuy, Bertram Glaß, Felix Keil, Wolfram Klapper, Maike Nickelsen, Heinz Schmidberger, Clemens A. Schmitt, Novak Urban. Onkopedia Leitlinie Diffuses grosszelliges B-Zell-Lymphom. Juli 2022.

4 Quality aspects

4.1 Drug substance

Epcoritamab is a bispecific humanised IgG1 monoclonal antibody (mAb) with specificity for CD20 (expressed on target B cells) and CD3 (expressed on effector T cells). Epcoritamab consists of 2 heavy chains (HC) and 2 light chains (LC), joined by disulphide bonds, and carries 1 N-linked biantennary complex-type glycan attached to each HC. Epcoritamab is prepared by controlled reduction and oxidation of 2 biological intermediate antibodies 3005a (IgG1-CD3-FEAL) and 3001d (IgG1 CD20-FEAR), resulting in an exchange of the Fab arms. The Fab-arm exchange was facilitated by amino acid substitutions in the CH3 domain of the parental mAb HC to promote Fab-arm exchange. The molecular weight of epcoritamab is approximately 149 kDa.
Each parental antibody is produced in a separate Chinese hamster ovary (CHO) cell line. For each production cell line a respective 2-tiered cell banking system of master cell bank (MCB) and working cell bank (WCB) is in place. The parental antibodies are manufactured separately.
After thawing of the respective WCB vial, the cells are grown in suspension culture in a series of seed train bioreactors to generate sufficient cell mass to seed the production bioreactor. The culture is harvested, and purification of the respective mAb is performed with dedicated chromatography and filtration steps. The 2 intermediates are stored and tested before being released for drug substance manufacturing. In a subsequent step, the 2 parental antibodies are combined, and their HC-HC disulphide bonds are selectively reduced, followed by oxidation to produce the heterodimeric epcoritamab antibody. The epcoritamab drug substance is purified using chromatography and ultrafiltration/diafiltration steps.
The entire manufacturing process for epcoritamab drug substance is validated with several consecutive batches, and the data demonstrated consistent production and efficient removal of impurities.
Several changes were implemented during development of the manufacturing process of the drug substance, including changes to the manufacturing site and production scale. However, the analytical comparability studies, which included batch release data, extended characterisation data and stress stability data, demonstrated comparability between the different processes.
The physicochemical and biological properties of the drug substance and its impurities were characterised using state-of-the-art methods.
The specifications for release include relevant tests and limits, e.g. for identity, purity and impurities, quantity, and potency. Specifications are based on clinical data and batch analysis (release and stability data), and are in conformance with current compendial or regulatory guidelines.
Batch analysis data from clinical and process validation batches were provided. All batch release data comply with the drug substance specifications, which were valid at the time of batch release. All specific analytical methods are described and were fully validated.
The drug substance is stored frozen. During storage, no changes were observed under the proposed storage conditions.

4.2 Drug product

Epcoritamab drug product is provided as a sterile, preservative-free liquid supplied in a single-dose vial. All used excipients (sodium acetate trihydrate, acetic acid, D-sorbitol, polysorbate 80 and water for injection) are of compendial grade. Epcoritamab drug product is manufactured in 2 strengths, 5 mg/mL and 60 mg/mL. The 5 mg/mL strength is supplied as a 4 mg/0.8 mL concentrate for solution for injection; the 60 mg/mL strength is supplied as a 48 mg/0.8 mL solution for injection.
Changes were also implemented for the drug product during manufacturing process development, e.g. different manufacturing sites and batch size. However, comparability assessments were executed, and all predefined comparability acceptance criteria were met.
The drug product manufacturing process consists of thawing and pooling of drug substance, formulation solution compounding (only for epcoritamab drug product 5 mg/mL), bioburden reduction filtration, sterile filtration, filling/stoppering, crimping, and visual inspection.
The drug manufacturing process was validated with 4 process performance qualification batches (2 for 5 mg/mL and 2 for 60 mg/mL). The data demonstrated a consistent production.

The specifications for release and stability of the drug products include relevant tests and acceptance criteria, e.g. for appearance, identity, purity and impurities, quantity, potency, pH, osmolality, visible and subvisible particles, extractable volume, bacterial endotoxins, and sterility. The drug product specifications comply with current compendial and regulatory guidelines.
Batch analysis data for several batches of the drug product, including clinical and process validation batches, were provided. All batch release data comply with the drug product specifications, which were valid at the time of batch release. All specific analytical methods are described and were fully validated.
The container closure system used for the 5 mg/mL and 60 mg/mL drug product is a 2R, borosilicate glass type I vial closed with a bromobutyl rubber and an aluminium seal with a flip-off disc. The materials of the type I glass vial and rubber stopper meet compendial requirements.
The vials are stored at 2°C to 8°C protected from light. The stability data support a shelf life of 24 months.

4.3 Quality conclusions

The manufacturing processes (drug substance and drug product) are well described and demonstrate a consistent quality of drug substance and drug product. The shelf life of the drug substance and drug product are supported by data from recommended storage conditions, as well as accelerated and stress studies. Safety concerns with regard to viral and non-viral contaminants were satisfactorily addressed. The risk for adventitious agents is minimised.

5 Nonclinical aspects

Regarding the marketing authorisation application for Tepkinly, the Division Nonclinical Assessment conducted an abridged evaluation, which was based on the CHMP assessment report (dated 20.07.2023) provided by the applicant.
Overall, the submitted nonclinical documentation is considered appropriate to support the approval of Tepkinly in the proposed indication. The pharmaco-toxicological profile has been sufficiently characterised.
The observed toxicity findings in nonclinical studies are consistent with the anticipated pharmacological activity of epcoritamab. Based on the mechanism of action and nonclinical data, cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome are considered important identified risks for human use.
The safety margins are low or nonexistent, which is acceptable for the proposed indication. All nonclinical data relevant for safety are adequately mentioned in the information for healthcare professionals.

6 Clinical aspects

6.1 Clinical pharmacology

The evaluation of the clinical pharmacology data of this application has been carried out in reliance on previous regulatory decisions by the EMA and FDA. The available assessment reports and corresponding product information from these authorities were used as a basis for the clinical pharmacology evaluation.

For further details concerning clinical pharmacology see the information for healthcare professionals in the appendix of this report.

6.2 Dose finding and dose recommendation

The epcoritamab starting dose level (0.004 mg) was chosen based on data from nonclinical studies. A fixed-dose approach was selected as T-cells (target effector cells for epcoritamab) were not expected to occur in different numbers according to body weight or body surface area. The subcutaneous (SC) route of epcoritamab administration was chosen based on its lower C_{max} value and lower peak cytokine levels, but comparable B-cell depletion compared to IV administration at the same doses in the nonclinical studies.

Dose finding for clinical use is based on the dose escalation part of study GCT3013-01. In total, 17 dosing regimens between 6 mg and 60 mg were tested in 68 patients. A review of data from the different cohorts indicated the proposed priming/intermediate/full dosing regimen of 0.16 mg/0.8 mg/48 mg regimen had similar or numerically lower rates of cytokine release syndrome (CRS). Based on clinical results, as well as pharmacokinetic modelling data, a schedule of a priming dose of 0.16 mg in Week 1, an intermediate dose of 0.8mg in Week 2, and a full dose of 48 mg for all subsequent applications was chosen.

In summary, the dose-finding part of trial GCT3013-01 and exposure-response analyses support 48 mg as a dose with acceptable efficacy and safety, but also indicated that other doses might be equally effective/safe.

6.3 Efficacy

The applicant submits results of the expansion cohort of the EPCORE NHL-1 trial (GCT3013-01), a Phase 1/2, open-label, dose-escalation trial of GEN3013 in patients with relapsed, progressive or refractory B-cell lymphoma, to support the marketing authorisation application for 3L+ DLBCL (schedule of a priming dose of 0.16 mg in Week 1, an intermediate dose of 0.8 mg in Week 2, and a full dose of 48 mg for all subsequent applications).

The first patient was included in June 2020. The data cut-off date for the submitted clinical efficacy and safety data was 30 June 2023. The trial is ongoing (estimated primary completion date January 2025, estimated study completion date April 2029).

The expansion cohort of the single-arm EPCORE NHL-1 trial included 157 patients with large B-cell lymphoma (LBCL). 52.9% patients (N=83) were from Europe. At the data cut-off date, 51 (32.5%) patients (including 47 DLBCL patients) were still receiving epcoritamab treatment.

The median number of prior lines of therapy was 3 (range: 2, 11), with 46 patients (29.3%) receiving 2, 50 patients (31.8%) receiving 3, and 61 patients (38.9%) receiving ≥4 prior lines of therapy. 96 patients (61.1%) had primary refractory disease and 119 patients (75.8%) were refractory to ≥2 consecutive lines of therapy. 130 patients (82.8%) were refractory to the last line of systemic therapy. 31 patients (19.7%) with LBCL had prior ASCT, 61 (38.9%) patients had received prior CAR T-cell therapy (including 46 of 61 patients who were refractory to CAR T-cell therapy).

The primary endpoint was overall response rate (ORR). ORR was 56.3% for the subgroup with prior CAR T-cell therapy or not eligible for CAR T-cell therapy (N=87). Median duration of response (DOR) for this subgroup was 15.6 months (4.0, NR). Of note, there was a high rate of censoring (about 60%).

Median overall survival (OS) was 14.7 months (8.2, NR) for this subgroup with a median follow-up period of 15.5 months.

6.4 Safety

The applicant submitted pooled safety data from 167 large B-cell lymphoma (LBCL) patients as the primary safety data for the marketing authorisation application. Median duration of treatment was 3.7 months (range: 0, 20) and median number of cycles of treatment administered was 5.0 (range 1, 22). The majority of patients (69.5%) received 3 or more cycles of treatment. 114 (68.3%) patients discontinued treatment, mostly because of disease progression (52.1%). 53 (31.7%) patients remained on epcoritamab treatment as of the data cutoff. Overall, 12 (7.2%) patients discontinued study treatment due to a treatment-emergent adverse event (TEAE).

In the safety pool, 166 patients (99.4%) experienced at least 1 TEAE. The most frequent TEAEs reported in ≥20% of patients included CRS, pyrexia, injection site reaction, neutropenia, nausea, and diarrhoea.

Grade ≥3 TEAEs were reported for 63% of patients. The most frequent grade 3 or 4 TEAEs reported in ≥5% of patients were neutropenia, anaemia, neutrophil count deceased, and thrombocytopenia.

89 patients (56.7%) experienced serious TEAEs. The most frequent serious TEAEs reported in ≥2% of patients included CRS, pleural effusion, febrile neutropenia, Immune effector cell-associated neurotoxicity syndrome (ICANS), pneumonia, pyrexia, and sepsis.

Fatal TEAEs were reported for 12 patients (7.2%); 1 of these fatal TEAEs was assessed as related to epcoritamab by the investigator (grade 5 ICANS event). COVID-19 and general physical health deterioration were reported for 2 patients; all other fatal TEAEs were reported in 1 patient each (COVID19 pneumonia, progressive multifocal leukoencephalopathy [PML], loss of consciousness, myocardial infarction, hepatotoxicity, malignant neoplasm progression, pulmonary embolism). The narratives of the grade 5 fatal events, other than the 1 case of ICANS, do not suggest a relation to the study drug.

Adverse events of special interest (AESIs) for epcoritamab treatment are CRS, ICANS, and clinical tumour lysis syndrome (CTLS).
Most patients had a maximum grade 1 (31%) or 2 (17%) CRS event. Five patients (3%) experienced a maximum grade 3 event. No grade 4 or grade 5 events of CRS were reported. CRS events generally occurred early in treatment. Overall, 10 patients (6.0%) experienced ICANS. In 7 patients, the ICANS overlapped with CRS events. All ICANS were considered treatment-related by the investigator, and most were grade 1 (4.2%) or grade 2 (1.2%) events. There were no grade 3 or 4 ICANS events, and there was 1 grade 5 event.

6.5 Final clinical benefit risk assessment

Diffuse large B-cell lymphoma (DLBCL) is the most frequent aggressive B-cell non-Hodgkin lymphoma (B-NHL), with an incidence of roughly 4/100,000/year in Europe[3]. Treatment options for

[3] Tilly H, Gomes da Silva M, Vitolo U, Jack A, Meignan M, Lopez-Guillermo A, Walewski J, André M, Johnson PW, Pfreundschuh M, Ladetto M; ESMO Guidelines Committee. Diffuse large B-cell lymphoma (DLBCL): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2015 Sep;26 Suppl 5:v116-25. doi: 10.1093/annonc/mdv304. PMID: 26314773.

relapsed/refractory disease after CAR T-cell therapy, or for patients who are ineligible for CAR T-cell therapy, are very limited.

The efficacy of epcoritamab in patients with r/r DLBCL after ≥ 2 prior systemic therapies and prior anti-CD19-CAR T-cell therapy, or who are ineligible for CAR T-cell therapy, is encouraging in this heavily pre-treated population.

The overall safety is manageable, and the most relevant safety risks of CRS and neurological toxicity including ICANS are described in the information for healthcare professionals.

Given the limitations associated with the uncontrolled single-arm design of the pivotal study and the small sample size, epcoritamab efficacy in DLBCL patients will need to be demonstrated in a comparative trial, and the safety profile needs to be confirmed in a larger patient cohort. Controlled data from the Phase 3 study GCT3013-05 were accepted as confirmatory results. GCT3013-05 is a randomised trial of epcoritamab versus standard of care in patients with relapsed or refractory DLBCL.

7 Risk management plan summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

8 Appendix

Approved information for healthcare professionals

Please be aware that the following version of the information for healthcare professionals for Tepkinly was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the information for healthcare professionals approved in one of the official Swiss languages.

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.
Tepkinly has been authorised temporarily, see “Indications/Uses” section.

TEPKINLY®, concentrate for solution for injection

Composition

Active substances

Epcoritamab (produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology).

Excipients

Sodium acetate trihydrate (corresponds to 0,48 mg sodium), acetic acid, sorbitol (E420) 21,84 mg, polysorbate 80, water for injection.

Pharmaceutical form and active substance quantity per unit

Concentrate for solution for injection
Each vial contains 4 mg epcoritamab in 0,8 ml solution (5 mg/ml).
Colourless to slightly yellow solution, pH 5.5 and osmolality of approximately 211 mOsm/kg.

Indications/Uses

Tepkinly is indicated as monotherapy for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), after two or more lines of systemic therapy, including a CD20 antibody, where patient is unable to receive or have previously received anti-CD19-targeted CAR-T cell therapy (see “Clinical efficacy” section).

This indication has been granted temporary authorisation as the clinical data were incomplete at the time the application was assessed (Art. 9a Therapeutic Products Act). The temporary authorisation is contingent on the timely fulfilment of conditions. After they have been met, the temporary authorisation can be converted into an ordinary authorisation.

Dosage/Administration

Tepkinly is for subcutaneous (SC) injection only. Tepkinly should only be administered under the supervision of a healthcare professional qualified in the use of anti-cancer therapies, in a setting with appropriate medical support to manage severe reactions such as cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS).
In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Monitoring

Monitor patients for potential CRS and/or immune effector cell-associated neurotoxicity syndrome (ICANS) following epcoritamab administration during Cycle 1 and in subsequent cycles.
Patients should be monitored within proximity of a healthcare facility (or alternatively in an inpatient setting) for signs and symptoms of CRS and/or ICANS for 24 hours for Cycle 1 Day 1 and Cycle 1 Day 8.
Patients should be hospitalized 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.
Intensive monitoring should be performed for the next administration of Tepkinly if CRS Grade 3 or clinically relevant neurological toxicities (e.g., serious or life-threatening neurological toxicities including ICANS) related to Tepkinly administration were observed during the previous administration. In these cases, inpatient monitoring should be performed for at least 72 hours and patients should be monitored daily for signs and symptoms of CRS, neurological and other toxicities for up to 7 days after administration of Tepkinly.
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”).

Posology

Recommended pre-medication and dose schedule

Administer Tepkinly according to the dosing schedule outlined in Table 1.
Tepkinly should be administered according to the following schedule in 28-day cycles (each cycle has 28 days):

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.			

Tepkinly should be administered until disease progression or unacceptable toxicity.
Patients should be well hydrated before using Tepkinly.

Details on recommended premedication for cytokine release syndrome (CRS) are shown in Table 2.

Table 2: Epcoritamab premedication

Cycle	Patient requiring premedication	Premedication	Administration
Cycle 1	All patients	Prednisolone (100 mg oral or intravenous) or equivalent	• 30-120 minutes prior to each weekly administration of epcoritamab • And for three consecutive days following the administration of epcoritamab in Cycle 1
		• Diphenhydramine (50 mg oral or intravenous) or equivalent • Paracetamol (650 to 1000 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 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 CRS of Grade 2 or higher
[a] Patients will be permanently discontinued from epcoritamab after a Grade 4 CRS event.			

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

Dose adjustment following undesirable effects

Cytokine release syndrome (CRS)

Patients treated with epcoritamab may develop Cytokine release syndrome (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 epcoritamab administration.

Table 3: CRS grading and management guidance

Grade[a]	Presenting Symptoms	Actions
Grade 1	**Temperature ≥ 38°C[b]**	• Withhold Tepkinly and manage per current practice guidelines. • Ensure CRS symptoms are resolved prior to next dose of Tepkinly.[c]
Grade 2	**Temperature ≥ 38°C[b] with:** Hypotension not requiring vasopressors and/or Hypoxia requiring low-flow oxygen[e] by nasal cannula or blow-by.	• Withhold Tepkinly and manage per current practice guidelines. • Ensure CRS symptoms are resolved prior to next dose of Tepkinly.[c] • Administer premedication[d] prior to next dose of Tepkinly. • For the next dose of Tepkinly, monitor more frequently and consider hospitalization.
Grade 3	**Temperature ≥ 38°C[b] with:** Hypotension requiring a vasopressor (with or without vasopressin) and/or Hypoxia requiring high-flow oxygen[e] by nasal cannula, face mask, non-rebreather mask, or Venturi mask.	• Withhold Tepkinly and manage per current practice guidelines, which may include intensive care. • Ensure CRS symptoms are resolved prior to the next dose of Tepkinly.[c] • Administer premedication[d] prior to next dose of Tepkinly. • Hospitalize for the next dose of Tepkinly.
		Recurrent Grade 3 CRS • Permanently discontinue Tepkinly.

Grade[a]	Presenting Symptoms	Actions
		• Manage CRS per current practice guidelines and provide supportive therapy, which may include intensive care.
Grade 4	**Temperature ≥ 38°C[b] with:** Hypotension requiring multiple vasopressors (excluding vasopressin) and/or Hypoxia requiring oxygen by positive pressure (e.g., CPAP, BiPAP, intubation and mechanical ventilation).	• Permanently discontinue Tepkinly. • Manage CRS per current practice guidelines and provide supportive therapy, which may include intensive care.

[a] Based on American Society for Transplantation and Cellular Therapy (ASTCT) 2019 grading for CRS.
[b] Premedication may mask fever, therefore if clinical presentation is consistent with CRS, follow these management guidelines.
[c] Refer to section "*Delayed administration*" for information on restarting Tepkinly after dosage delays (see "Dosage/Administration")
[d] If Grade 2 or 3 CRS occurs with the second full dose (48 mg) or beyond, administer CRS premedications with each subsequent dose until a Tepkinly dose is given without subsequent CRS of Grade 2 or higher. Refer to Table 2 for additional information on premedication.
[e] Low-flow oxygen defined as oxygen delivered at < 6L/minute; high-flow oxygen defined as oxygen delivered at ≥ 6 L/minute.

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]	Presenting Symptoms[b]	Actions
Grade 1	ICE score 7-9[c], Or depressed level of consciousness[d]: awakens spontaneously.	• Withhold Tepkinly until ICANS resolves.[e] • Monitor neurologic symptoms and consider consultation with neurologist and other specialists for further evaluation and management, including consideration for starting non-sedating, anti-seizure medicines for seizure prophylaxis. • If an ICANS should occur, manage it according to the current practice guidelines.
Grade 2	ICE score 3-6[c], Or depressed level of consciousness[d]: awakens to voice.	• Withhold Tepkinly until ICANS resolves.[e] • Administer dexamethasone[f] 10 mg intravenously every 6 hours. Continue dexamethasone use until resolution to Grade 1 or less, then taper. • Monitor neurologic symptoms and consider consultation with neurologist and other specialists for further evaluation and management, including consideration for starting non-sedating, anti-seizure medicines for seizure prophylaxis. • If an ICANS should occur, manage it according to the current practice guidelines.
Grade 3	ICE score 0-2[c], Or depressed level of consciousness[d]: awakens only to tactile stimulus, Or seizures,[d] either: • Any clinical seizure, focal or generalized, that resolves rapidly, or	First Occurrence of Grade 3 ICANS • Withhold Tepkinly until ICANS resolves.[e] • Administer dexamethasone[f] 10 mg intravenously every 6 hours. Continue dexamethasone use until resolution to Grade 1 or less, then taper. • Monitor neurologic symptoms and consider consultation with neurologist and other specialists for further evaluation and management, including consideration for starting non-sedating, anti-seizure medicines for seizure prophylaxis.

Grade[a]	Presenting Symptoms[b]	Actions
	• Non-convulsive seizures on electroencephalogram (EEG) that resolve with intervention, Or raised intracranial pressure: focal/local edema on neuroimaging.[d]	• Provide supportive therapy, which may include intensive care. • If an ICANS should occur, manage it according to the current practice guidelines.
		Recurrent Grade 3 ICANS • Permanently discontinue Tepkinly. • Administer dexamethasone[f] 10 mg intravenously every 6 hours. Continue dexamethasone use until resolution to Grade 1 or less, then taper. • Monitor neurologic symptoms and consider consultation with neurologist and other specialists for further evaluation and management, including consideration for starting non-sedating, anti-seizure medicines for seizure prophylaxis. • Provide supportive therapy, which may include intensive care. • If an ICANS should occur, manage it according to the current practice guidelines.
Grade 4	ICE score 0[c], Or depressed level of consciousness[d]: either: • Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse, or • Stupor or coma Or seizures,[d] either: • Life-threatening prolonged seizure (> 5 minutes), or	• Permanently discontinue Tepkinly. • Administer dexamethasone[f] 10 mg intravenously every 6 hours. Continue dexamethasone use until resolution to Grade 1 or less, then taper. • Alternatively, consider administration of methylprednisolone 1,000 mg per day intravenously and continue methylprednisolone 1,000 mg per day intravenously for 2 or more days.

Grade[a]	Presenting Symptoms[b]	Actions
	• Repetitive clinical or electrical seizures without return to baseline in between, Or motor findings[d]: • Deep focal motor weakness, such as hemiparesis or paraparesis, or raised intracranial pressure/cerebral edema,[d] with signs/symptoms such as: • Diffuse cerebral edema on neuroimaging, or • Decerebrate or decorticate posturing, or • Cranial nerve VI palsy, or • Papilledema, or • Cushing's triad.	• Monitor neurologic symptoms and consider consultation with neurologist and other specialists for further evaluation and management, including consideration for starting non-sedating, anti-seizure medicines for seizure prophylaxis. • Provide supportive therapy, which may include intensive care. • If an ICANS should occur, manage it according to the current practice guidelines.

[a] Based on American Society for Transplantation and Cellular Therapy (ASTCT) 2019 grading for ICANS.

[b] Management is determined by the most severe event, 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 (names 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] Not attributable to any other cause.

[e] Refer to section "Delayed administration" for information on restarting Tepkinly after dosage delays (see "Dosage/Administration").

[f] All references to dexamethasone administration are dexamethasone or equivalent.

Table 5: Recommended Dosage Modifications for Other Adverse Reactions

Adverse Reaction[1]	Severity[1]	Action
Infections (see "Warnings and Precautions")	Grades 1-4	• Withhold Tepkinly in patients with active infection, until the infection resolves.[2] • For Grade 4, consider permanent discontinuation of Tepkinly.
Neutropenia (see "Warnings and Precautions")	Absolute neutrophil count less than 0.5 x 10^9/L	• Withhold Tepkinly until absolute neutrophil count is 0.5 x 10^9/L or higher.[2]
Thrombocytopenia (see "Warnings and Precautions")	Platelet count less than 50 x 10^9/L	• Withhold Tepkinly until platelet count is 50 x 10^9/L or higher.[2]
Other Adverse Reactions (see "Adverse Reactions")	Grade 3 or higher	• Withhold Tepkinly until the toxicity resolves to Grade 1 or baseline.[2]
[1] Based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 5.0. [2] For recommendations on restarting Tepkinly after dosage delays see "Delayed administration".		

Delayed administration

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).

Special dosage instructions

Patients with renal disorders

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.

Patients with hepatic disorders

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.

Children and adolescents

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

Elderly patients

In patients with DLBCL in EPCORE NHL-1, 44 (32%) were ≥65 to <75 years of age and 29 (21%) patients 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.

Mode of administration

Tepkinly should be administered by subcutaneous injection, preferably in the lower part of the abdomen or the thigh. Change of injection site from left or right side or vice versa is recommended especially during the weekly administration (Cycles 1-3).
For instructions on dilution of the medicinal product before administration, see “Instructions for dilution and administration”.

Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Warnings and precautions

Cytokine release syndrome (CRS)

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 dyspnoea.

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 20.2 hours (range: 0.2 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/Administration”).
Monitor patients for potential CRS following epcoritamab administration during Cycle 1 and in subsequent cycles as needed at the physician’s discretion.
Patients should be monitored within proximity of a healthcare facility (or alternatively in an inpatient setting) for signs and symptoms of CRS and/or ICANS for 24 hours for Cycle 1 Day 1 and Cycle 1 Day 8.
Patients should be hospitalized 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.
At the first signs or symptoms of CRS manage according to applicable practice guidelines. 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/Administration”).

Neurologic events including immune effector cell-associated neurotoxicity syndrome (ICANS)

Tepkinly can cause serious or life-threatening neurologic side effects, including immune effector cell-associated neurotoxicity syndrome (ICANS). ICANS may manifest as aphasia, altered level of consciousness, impairment of cognitive skills, motor weakness, seizures, and cerebral oedema.
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 to 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 administration during Cycle 1 and in subsequent cycles as needed at the physician’s discretion.
Patients should be monitored within proximity of a healthcare facility (or alternatively in an inpatient setting) for signs and symptoms of CRS and/or ICANS for 24 hours for Cycle 1 Day 1 and Cycle 1 Day 8.
Patients should be hospitalized 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.At the first signs or symptoms of ICANS manage according to applicable practice guidelines. Counsel patients on the signs and symptoms of ICANS and that the onset of events may be delayed. Instruct patients to contact their healthcare professional and seek immediate medical attention should signs or symptoms occur at any time. Delay or discontinue epcoritamab as recommended (see “Dosage/Administration”).

Serious infections

Treatment with epcoritamab may lead to an increased risk of infections. Serious infections, including fatal infections, were observed in patients treated with epcoritamab in clinical trials (see “Adverse Events”).
Avoid administration of epcoritamab in patients with clinically significant active systemic infections. As appropriate, administer prophylactic antimicrobials (see “Dosage/Administration”). Monitor patients for signs and symptoms of infections prior to and during treatment and treat according to standard/local guidelines and practice.

Hepatotoxicity

Elevated liver enzymes have been reported in patients treated with Epcoritamab (see “Undesirable effects”). Monitor liver enzymes and bilirubin at initiation and during treatment, if clinically indicated. Use local protocols/guidelines as appropriate for treatment.

Reactivation of hepatitis B

Reactivation may occur in patients treated with drugs directed against B cells of hepatitis B virus (HBV), which can lead to fulminant hepatitis and liver failure, sometimes even death. Patients with positive HBV serology should be monitored for clinical symptoms indicating HBV reactivation and laboratory tests should be carried out during treatment with Tepkinly.

Cytopenias

Tepkinly can cause serious or severe cytopenias, including neutropenia, anemia, and thrombocytopenia (see “Undesirable effects”).
Monitor complete blood counts throughout treatment. Based on the severity of cytopenias, temporarily withhold or permanently discontinue Tepkinly (see “Dosage/Administration”). Consider prophylactic granulocyte colony-stimulating factor administration as applicable.

Immunisation

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

Excipients with known effect

This medicinal product contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially ‘sodium-free’.
This medicinal product contains 21.84 mg of sorbitol per vial. Patients with hereditary fructose intolerance (HFI) should not receive this medicine unless absolutely necessary.

Interactions

No interaction studies have been performed.

CYP substrates

For certain CYP substrates, minimal changes in the concentration may lead to serious adverse reactions. Monitor for toxicity or drug concentrations of such CYP substrates when co-administered with Tepkinly.
Epcoritamab causes release of cytokines that may suppress activity of CYP enzymes, resulting in increased exposure of CYP substrates. Increased exposure of CYP substrates is more likely to occur after the first dose of Tepkinly on Cycle 1 Day 1 and up to 14 days after the first 48 mg dose on Cycle 1 Day 15, and during and after CRS (see “Warnings and Precautions”).

Pregnancy, lactation

Women of childbearing potential

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

Pregnancy

There are no data on the use of epcoritamab in pregnant women. Animal reproduction studies have not been conducted with epcoritamab 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. IgG1 antibodies, such as epcoritamab, can cross the placenta resulting in foetal exposure. Advise pregnant women of the potential risk to a foetus.
Epcoritamab is not recommended during pregnancy and in women of childbearing potential not using contraception.
Verify pregnancy status in females of reproductive potential prior to initiating epcoritamab treatment.

Lactation

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

The effect of epcoritamab on male and female fertility is unknown. Animal studies with epcoritamab showed no effect on reproductive organs that would indicate impaired fertility. No fertility studies have been conducted with epcoritamab (see “Preclinical data”).

Effects on ability to drive and use machines

No formal studies on the effect of epcoritamab 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, cycling or using heavy or potentially dangerous machines.

Undesirable effects

Summary of the safety profile

The safety of epcoritamab was evaluated in a non-randomised, single-arm study in 167 patients with relapsed or refractory LBCL 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 median duration of exposure to epcoritamab was 3.7 months (range: 0 to 25 months).
The most common adverse reactions (≥ 20%) were CRS, neutropenia, injection site reactions, pyrexia, nausea and diarrhoea.
Serious adverse reactions occurred in 43% of patients. The most frequent serious adverse reaction (≥10%) was cytokine release syndrome (31%). Three patients (1.8%) experienced a fatal adverse reaction of pneumonia and one patient (0.6%) experienced a fatal adverse reaction of ICANS.
Adverse reactions that led to discontinuation occurred in 4.8% of patients. Discontinuation of epcoritamab due to pneumonia occurred in 6 patients (3.6%) while CRS or ICANS occurred in 1 patient (0.6%) each.
Dose delays due to adverse reactions occurred in 22% of patients. Adverse reactions leading to dose delays (≥ 3%) were CRS (7.2%), neutropenia (4.8%), pyrexia (3.0%), and thrombocytopenia (3.0%).

List of adverse reactions

The adverse reactions of any grade listed below are based on pooled data from patients in the EPCORE NHL-1 (escalation and expansion cohort) and EPCORE NHL-3 study (N=431).

Adverse reactions are listed by MedDRA system organ class and are based on the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1 000); and very rare (< 1/10 000).

Blood and lymphatic system disorders
Very Common: Neutropenia[a] (30%), Anemia[b] (17%), Thrombocytopenia[c] (17%)
Common: Febrile neutropenia

Infections and infestations
Very Common: Pneumonia[d] (10%)
Common: Upper respiratory tract infections[e]

Neoplasm benign, malignant and unspecified (including cysts and polyps)
Common: Tumor flare

Gastrointestinal disorders
Very Common: Diarrhea (19%), Nausea (18%)
Common: Vomiting

General disorders and administration site conditions
Very Common: Injection site reactions[f] (40%), Pyrexia[g] (21%)

Immune system disorders
Very Common: Cytokine release syndrome (63%)

Metabolism and nutrition disorders
Very Common: Decreased appetite (11%)
Common: Hypophosphatemia, hypokalemia, hypomagnesemia, tumor lysis syndrome

Nervous system disorders
Very Common: Headache (12%)
Common: Immune effector cell-associated neurotoxicity syndrome (ICANS)

Skin and subcutaneous tissue disorders
Very Common: Rash[h] (14%)
Common: Pruritus

Investigations
Common: Alanine aminotransferase increased, aspartate aminotransferase increased, blood creatinine increased, blood sodium decreased[i], alkaline phosphatase increased

Events were graded using NCI CTCAE version 5.0; CRS and ICANS events were graded using ASTCT consensus criteria (Lee et. al., 2019). Tumor lysis syndrome events were graded based on Cairo-Bishop.
[a] Neutropenia includes neutropenia and neutrophil count decreased.
[b] Anemia includes anemia, haemoglobin decreased, and serum ferritin decreased.
[c] Thrombocytopenia includes platelet count decreased and thrombocytopenia.
[d] Pneumonia includes COVID-19 pneumonia and pneumonia.
[e] Upper respiratory tract infections include laryngitis, pharyngitis, respiratory syncytial virus infection, rhinitis, rhinovirus infection, and upper respiratory tract infection.
[f] Injection site reactions include injection site bruising, injection site erythema, injection site hypertrophy, injection site inflammation, injection site mass, injection site oedema, injection site pain,

injection site pruritus, injection site rash, injection site reaction, injection site swelling, and injection site urticaria.

[g] Pyrexia includes body temperature increased and pyrexia.

[h] Rash includes exfoliative rash, rash, rash erythematous, rash maculo-papular, rash papular, rash pruritic, rash pustular, and rash vesicular.

[i] Blood sodium decreased includes blood sodium decreased and hyponatraemia.

Description of specific adverse reactions and additional information

Cytokine release syndrome

CRS of any grade occurred in 51% (85/167) of patients treated with epcoritamab. The incidence of Grade 1 was 31% (51/167), Grade 2 was 17% (29/167), and Grade 3 occurred in 3.0% (5/167). The median time to onset of CRS from the most recent administered epcoritamab dose was 2 days (range: 1 to 11 days). CRS resolved in 98.4% of patients, and the median duration of CRS events was 2 days (range 1 to 27 days).

Of the 85 patients that experienced CRS, the most common signs and symptoms of CRS included pyrexia 99%, hypotension 31% and hypoxia 19%. Other signs and symptoms of CRS in greater than two patients included chills (11%), tachycardia (including sinus tachycardia (9%)), dyspnoea (3.5%), and headache (3.5%). Transient elevated liver enzymes (ALT or AST > 3xULN) were concurrent with CRS in 2.4% of patients with CRS. See ”Dosing/Administration” and “Warnings and Precautions” for monitoring and management guidance.

Immune effector cell-associated neurotoxicity syndrome

ICANS occurred in 6% of patients treated with epcoritamab; 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 epcoritamab 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 epcoritamab. The most frequent serious infections were pneumonia (2.4%), sepsis (2.4%), COVID-19 (1.8%), COVID-19-pneumonia (1.8%), bacteraemia (1.2%), septic shock (1.2%), and upper respiratory tract infection (1.2%). Fatal serious infections occurred in 4 (2.4%) patients.

Tumor lysis syndrome
TLS occurred in 1.8% of patients. There was one patient who experienced onset on Day 14 with resolution on Day 17. Two additional patients experienced onset on Day 8 and Day 33 and both events were ongoing at the time of death; the deaths were due to disease progression.

Cytopenias
Neutrophil count decreased, hemoglobin decreased, and platelets decreased occurred in 51.3%, 61.8%, and 50.3% of patients, respectively. Grade 3 or 4 neutrophil count decreased, hemoglobin decreased, and platelets decreased occurred 33.2%. 13.3%, and 12.8% of patients, respectively.

CLIPPERS
One Grade 3 event of CLIPPERS occurred in 1 patient who was reported to have had CLIPPERS 106 days prior to the start of epcoritamab treatment.

Progressive multifocal leukoencephalopathy (PML)
PML occurred in two patients, of which 1 event of PML was fatal.

Immunogenicity
Anti-drug antibodies (ADA) were commonly detected. The incidence of treatment-emergent ADAs at the approved 48 mg dosing regimen in the target DLBCL population was 2.9% (2.9% positive, 2.9% indeterminate and 94.3% negative, N=140 evaluable patients) and 2.6% **(**2.6% positive, 2.6% indeterminate and 94.9% negative, N= 39 evaluable patients), in studies EPCORE NHL-1and EPCORE NHL-3, respectively. No evidence of ADA impact on pharmacokinetics, efficacy or safety was observed, however, data are still limited. Neutralising antibodies were not evaluated.

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 (79.1%), neutrophil count decreased (33.2%), haemoglobin decreased (13.3%), and platelets decreased (12.8%).

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

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

Properties/Effects

ATC code

L01FX27

Mechanism of action

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

Pharmacodynamics

Epcoritamab induced depletion of circulating Bcells (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. There were 21% subjects (n=33) 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. 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 , however elevations of cytokines could also be observed after Cycle 1.

Clinical efficacy

Study EPCORE NHL-1 was an open-label, multi-cohort, multicentre, single-arm trial that evaluated epcoritamab as monotherapy in patients with relapsed or refractory large B-cell lymphoma (LBCL) after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL). The study excluded patients with CNS involvement of lymphoma**,** allogeneic HSCT or solid organ transplant, chronic ongoing infectious diseases, any patients with known impaired T-cell immunity, a creatinine clearance of less than 45 ml/min, alanine aminotransferase >3 times the upper limit of normal and cardiac ejection fraction less than less than 45%. Efficacy was evaluated in 139 patients with DLBCL who had received the 48 mg full dose SC in cycles of 4 weeks, i.e., 28 days. Epcoritamab monotherapy was administered 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 6.

Table 6: 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
DLBCL Disease history (%)	
De Novo DLBCL	70
DLBCL transformed from indolent lymphoma	29
FISH Analysis Per Central 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 prior anti-CD20 therapy	84
Refractory to CAR-T	28
[a]A patient is considered to be primary refractory if they are refractory to frontline anti-lymphoma therapy. [b]A patient is considered to be refractory if they experience disease progression or stable disease as best response or disease progression within 6 months after therapy completion. Data cut: 31 Jan 2022	

Efficacy was established based on overall response rate (ORR) determined by Lugano criteria (2014) as assessed by Independent Review Committee (IRC). The median follow-up time was 15.5 months (range: 0.3 to 21 months) in patients with DLBCL who had prior CAR-T or who were not eligible for CAR-T.

Table 7: Efficacy results in study EPCORE NHL-1 in patients with DLBCL who had prior CAR-T or who were not eligible for CAR-T

Endpoint **IRC assessment**	**Epcoritamab** **(N=87)**
ORR[a], n (%)	49 (56)
(95% CI)	(45.3, 66.9)
CR, n (%)	27 (31)
(95% CI)	(21.5, 41.9)
PR, n (%)	22 (25)
DOR	
Median (95% CI), months	15.6 (4.0, NR)
DOR if Best Response is CR	
Median (95% CI), months	15.6 (15.6, NR)
CI = confidence interval; CR = complete response; DOR = duration of response; IRC = independent review committee; NR = not reached; ORR = overall response rate [a] Determined by Lugano criteria (2014) as assessed by independent review committee (IRC)	

The median time to CR was 2.8 months (range: 1.2 to 10.2 months).

Response durations were longer in patients who achieved CR, as compared to patients with a best response of partial remission (PR) (Table 7).
Median overall survival (OS) for patient on epcoritamab was 14.7 (8.2, not reached).

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 characterised by inter-individual variability (IIV) ranging from 25.7% to 137.5% coefficient of variation (CV) for epcoritamab PK parameters.
Epcoritamab maximum concentration (11.1 mcg/mL [41.5%]) is achieved after the first dose of the Q2W regimen (i.e., after the 11th dose of 48 mg at the first dose of Cycle 4). PK exposures are summarized for the recommended dosage of epcoritamab in Table 8.

Table 8: Exposure Parameters of Epcoritamab-bysp in Subjects with Relapsed or Refractory LBCL

	C_{avg} (mcg/mL)[1]	**C_{max} (mcg/mL)[1]**	**C_{trough} (mcg/mL)[1]**
First full 48 mg dose	1.6 (72.4)	2.2 (70.0)	1.7 (74.0)
End of weekly dosing (end of Cycle 3)	9.9 (45.1)	10.8 (41.7)	8.4 (53.3)
End of every 2-week dosing (end of Cycle 9)	5.9 (49.3)	7.5 (41.1)	4.1 (73.9)
Steady state[2] with every 4-week dosing	2.7 (69.5)	4.8 (51.6)	1.2 (130)
[1] Values are geometric mean with geometric CV% [2] Steady state values are approximated at Cycle 15 (Week 60)			

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 the apparent volume of distribution at steady state is 25.61 L (81.8%) based on population PK modelling.

Metabolism

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.

Kinetics in specific patient groups

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

Children and adolescents

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

Preclinical data

Repeated dose toxicity

Effects in the repeat-dose toxicity studies in cynomolgus monkeys were generally consistent with the pharmacologic mechanism of action of epcoritamab. 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/Carcinogenicity

Genotoxicity and carcinogenicity of epcoritamab were not examined.

Reproductive toxicity

Animal fertility studies have not been conducted with epcoritamab, however, in an intravenous general toxicity study of 5 weeks duration, epcoritamab caused no toxicological changes in the reproductive organs of male or female cynomolgus monkeys at doses up to 1 mg/kg/week. 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.

Other information

Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

Shelf life

Do not use this medicine after the expiry date ("EXP") stated on the pack.

Shelf life after opening

Chemical and physical in-use stability has been demonstrated for 24 hours at 30 °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. Within these 24 hours, the epcoritamab solution can be stored at room temperature for 12 hours from the time of preparation to administration.
Minimise exposure to daylight.
Allow epcoritamab solution to equilibrate to room temperature before administration.
Discard unused epcoritamab solution beyond the allowable storage time.

Special precautions for storage

Store in the refrigerator (2-8 °C).
Do not freeze.
Do not shake.
Keep the container in the outer carton in order to protect the contents from light.
Keep out of the reach of children.

Instructions for handling

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

Instructions for dilution and administration

The administration of epcoritamab takes place over the course of 28-day cycles, following the dosing schedule in “Dosage/Administration”. Tepklinly, concentrate for solution for injection must be used to prepare the loading dose (0.16 mg) and the intermediate dose (0.8 mg). For the full dose (48 mg) use Tepkinly, solution for injection.
Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Methods of dose preparation

Use aseptic technique to prepare the priming and intermediate dose of Tepkinly. Filtration of the diluted solution is not required.

Preparation instructions for 0.16 mg and 0.8 mg doses of epcoritamab

0.16 mg priming dose preparation instructions – 2 dilutions required

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 concentrate vial from the refrigerator. b) Allow the vial to come to room temperature for no more than 1 hour c) Gently swirl the epcoritamab vial. **DO NOT** invert, vortex, or vigorously shake the vial.
2)	Perform first dilution a) Label an appropriately sized empty vial as **"dilution A"**. b) Transfer **0.8 ml of epcoritamab** into the vial labelled as **dilution A**. c) Transfer **4.2 ml of 0.9% sodium chloride injection**, sterile solution, into the vial labelled as **dilution A**. 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 **2.0 ml of solution** from the vial labelled as **dilution A** into the vial labelled as **dilution B**. The **dilution A** vial is no longer needed. c) Transfer **8.0 ml of 0.9% sodium chloride injection**, sterile solution, into the vial labelled as **dilution B** 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 **1.0 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.
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

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

DO NOT invert, vortex, or vigorously shake the vial.	
2)	Perform dilution a) Label an appropriately sized empty vial as **"dilution A"**. b) Transfer **0.8 ml of epcoritamab** into the vial labelled as **dilution A**. c) Transfer **4.2 ml of 0.9% sodium chloride injection**, sterile solution, into the vial labelled as **dilution A** 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 **1.0 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.
5)	Discard the vial and any unused portion of epcoritamab in accordance with local requirements.

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).

Authorisation number

69161 (Swissmedic)

Packs

Tepkinly, concentrate for solution for injection: 1 vial of 4 mg/0.8 ml [A]

Marketing authorisation holder

AbbVie AG, 6330 Cham

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December 2023