Australian Government
Department of Health, Disability and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for EPKINLY

Active ingredient: Epcoritamab

Sponsor: AbbVie Pty Ltd

June 2025

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, Disability and Ageing and is responsible for regulating therapeutic goods, including medicines, medical devices, and biologicals.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety, and efficacy.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to the Australian public outweigh any risks associated with the use of therapeutic goods.
- The TGA relies on the public, healthcare professionals and industry to report problems with therapeutic goods. The TGA investigates reports received to determine any necessary regulatory action.
- To report a problem with a therapeutic good, please see the information on the TGA website.

About AusPARs

- The Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission. Further information can be found in Australian Public Assessment Report (AusPAR) guidance.
- AusPARs are prepared and published by the TGA.
- AusPARs are static documents that provide information that relates to a submission at a particular point in time. The publication of an AusPAR is an important part of the transparency of the TGA's decision-making process.
- A new AusPAR may be provided to reflect changes to indications or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

List of abbreviations

Abbreviation	Meaning
ABC	activated B-cell
ADA	antidrug antibody
aNHL	aggressive B-cell non-Hodgkin lymphoma
ARTG	Australian Register of Therapeutic Goods
ASA	Australia-specific annex
AUC_{inf}	area under the concentration-time profile from time zero extrapolated to infinite time
AUCτ	area under the concentration-time profile from time zero to time tau (τ), the dosing interval
B-NHL	B-cell non-Hodgkin lymphoma
CL/F	clearance
C_{max}	maximum plasma concentration
CMI	Consumer Medicines Information
CTLS	clinical tumour lysis syndrome
CR	complete response
CRS	cytokine release syndrome
DLBCL	diffuse large B-cell lymphoma
DOCR	duration of complete response
DOR	duration of response
ECOG	Eastern Cooperative Oncology Group
FL	follicular lymphoma
ESC	dose escalation phase
EXP	dose expansion phase
GCB	germinal centre B-cell
IRC	Independent Review Committee
iNHL	indolent B-cell non-Hodgkin lymphoma
LBCL	large B-cell lymphoma
MCL	mantle cell lymphoma
MRD	minimal residual disease
NOS	not otherwise specified
OR	overall response
ORR	overall response rate

Abbreviation	Meaning
PD	pharmacodynamic(s)
PI	Product Information
PK	pharmacokinetic(s)
popPK	population pharmacokinetic(s)
PR	partial response
PSUR	periodic safety update report
RP2D	recommended phase 2 dose
QW	once weekly dosing
Q2W	once every two weeks dosing
Q4W	once every four weeks dosing
RMP	risk management plan
R/R	relapsed or refractory
SAE	serious adverse event
TEAE	treatment emergent adverse event
TGA	Therapeutic Goods Administration
T_{max}	time to maximum concentration
TTCR	time to complete response
TTR	time to response
Vc/F	central volume of distribution

EPKINLY (Epcoritamab) submission

Type of submission:	New biological entity
Product name:	EPKINLY
Active ingredient:	Epcoritamab
Decision:	Approved
Date of decision:	19 February 2024
Date of entry onto ARTG:	6 January 2025
ARTG numbers:	EPKINLY epcoritamab 48mg/0.8mL solution for injection vial (404977) EPKINLY epcoritamab 4mg/0.8mL concentrate solution for injection vial (404978)
▼*Black Triangle Scheme*	Yes
Sponsor's name and address:	Abbvie Pty Ltd, 241 O'Riordan Street, Mascot NSW 2020
Dose form:	Sterile, preservative free, clear to slightly opalescent, colourless to slightly yellow solution
Strength:	EPKINLY 4 mg/0.8 mL concentrate solution for injection: Each 0.8 mL single-dose vial contains 4 mg of epcoritamab. EPKINLY 48 mg/0.8 mL solution for injection: Each 0.8 mL single-dose vial contains 48 mg of epcoritamab.
Container:	Type I glass vial with bromobutyl rubber stopper and aluminum seal with plastic flip off cap. The vial stopper is not made with natural rubber latex
Pack size:	1 vial
Approved therapeutic use for the current submission:	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. EPKINLY is not indicated for the treatment of patients with primary central nervous system lymphoma. This medicine has provisional approval in Australia for the treatment of adult patients with relapsed or refractory DLBCL after two or more lines of systemic therapy. The decision to approve this indication has been made on the basis of overall response and duration of response from an uncontrolled, open label phase I/II study. Continued approval of this indication depends on verification and description of benefit in confirmatory trials.
Route of administration:	Subcutaneous (SC) injection
Dosage:	Administer EPKINLY according to the following schedule in 28-day cycles (see table below). The EPKINLY dosing schedule includes an initial priming dose of 0.16 mg on Cycle 1 Day 1, an intermediate dose of 0.8 mg on Cycle 1 Day 8, and a full dose of 48 mg administered from Cycle 1 Day 15 and onwards,

according to the table below. Administer EPKINLY until disease progression or unacceptable toxicity.

Dosing schedule

Dosing schedule	Cycle of treatment	Days	Epcoritamab dose (mg)[a]
Weekly	Cycle 1	1	0.16 mg (Priming dose)
		8	0.8 mg (Intermediate dose)
		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.

For further information regarding dosage, refer to the Product Information.

Pregnancy category: Category C

Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible.

The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. The pregnancy database must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your state or territory.

Proposed indication

This AusPAR describes the submission by AbbVie Pty Ltd (the Sponsor)[1] to register EPKINLY - Epcoritamab for the following proposed indication:[2]

> *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.*

Diffuse large B-cell lymphoma

Diffuse large B-cell lymphoma (DLBCL) is the most common form of non-Hodgkin lymphoma (NHL), accounting for approximately 30% of cases, and 80% of aggressive lymphomas.[3] DLBCL is a heterogeneous group of biologically distinct entities resulting in clonal proliferation of a germinal or post-germinal B-cells.[4]

The 2016 WHO classification includes the following subtypes of B-cell lymphoma[5]:

- DLBCL not otherwise specified (NOS), which is further divided into the following subtypes:
  - Germinal centre B-cell (GCB),
  - Activated B-cell (ABC),
  - and Unclassified subtypes.
- T-cell/histiocyte-rich large B-cell lymphoma
- Primary DLBCL of the central nervous system
- Epstein-Barr virus positive DLBCL
- Epstein-Barr virus mucocutaneous ulcer
- DLBCL associated with chronic inflammation
- Primary cutaneous DLBCL, leg type.

Around 80% of all DLBCL is DLBCL, NOS. The GCB subtype has a gene expression profile similar to normal germinal centre B-cells with intraclonal heterogeneity, ongoing somatic hypermutation and CD10 and BCL6 expression. The ABC subtype has a gene expression more typical of post-germinal or activated B cells with high expression and activation of nuclear factor kappa B and expression of IRF4 and BCL2. The unclassified subtype account for 10-15% of cases. In general, the ABC subtype is associated with worse outcomes with standard chemotherapy.[6]

Subgroups can also be identified by molecular features. Between 10% and 1% of newly diagnosed DLBCL patients have a MYC proto-oncogene rearrangement, which results in

[1] A Sponsor is a person or company who does one or more of the following: a) exports therapeutic goods from Australia, b) imports therapeutic goods into Australia, c) manufactures therapeutic goods for supply in Australia or d) elsewhere arranges for another party to import, export or manufacture therapeutic goods

[2] This is the original indication proposed by the Sponsor when the TGA commenced the evaluation of this submission. It may differ to the final indication approved by the TGA and registered in the Australian Register of Therapeutic Goods.

[3] National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. B-cell Lymphomas. Version 3.2022 Available from: https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf

[4] Sunsanibar-Adaniya and Barta SK. 2021 Update on Diffuse Large B-cell lymphoma: A review of current data and potential applications on risk stratification and management Am J Hematol 2021; 96(5):617-629

[5] Gisselbrecht C, Van Den Neste E. How I manage patients with relapsed/refractory diffuse large B cell lymphoma. Br J Haematol. 2018; 182 (5): 633-643.

[6] Nowakowski GS, Czuczman MS. ABC, GCB, and double-hit diffuse large B-cell lymphoma: does subtype make a difference in therapy selection? Am Soc Clin Oncol Educ Book. 2015;e449–e457

dysregulated cellular survival and proliferation. This c-MYC proto-oncogene is located on chromosome 8q24. About half of these cases also carry a rearrangement of BCL2, an anti-apoptotic proto-oncogene and/or its transcription repressor BCL6. The presence of MYC with BCL2 ± BCL6 are the features of High-grade B-cell lymphoma – double hit or triple hit (HGBCL-DH/TH).[7] These features indicate a more aggressive DLBCL that is likely to have a worse outcome with front-line R-CHOP. They tend to be found more commonly in the GCB subtype. Patients with DLBCL can also have a double expresser lymphoma (DEL), with overexpression of the c-MYC oncogene and BCL2. DELs account for about 1/3 of new cases, are found in about ½ the cases that relapse or are refractory and tend to be more common in the ABC subtype.[8]

The occurrence of DLBCL increases with age and the median at onset is approximately 60-70 years. The disease is slightly more common in males. About 70% of patients have lymph node disease, and 30% extranodal disease.

Prior to treatment the diagnosis, staging and risk assessment are required. A morphological diagnosis of DLBCL should be confirmed in all cases by immunophenotypic investigations, either immunohistochemistry (IHC) or flow cytometry or a combination of both techniques. Based on recent consensus recommendations for staging and restaging of lymphoma developed by the clinical and imaging working groups of the international conference of malignant lymphomas (Lugano classification), fluorodeoxyglucose positron emission tomography (FDG-PET)/computed tomography (CT) scan is recommended as the gold standard for staging DLBCL patients. The staging is established according to the Ann Arbor classification system.

Adverse prognostic factors include Ann Arbor Stage III/IV disease, age > 60 years, elevated serum lactate dehydrogenase (LDH), Eastern Cooperative Oncology Group [ECOG] performance status ≥2, and extensive extranodal involvement. Three scoring systems incorporate these clinical parameters into prognostic scores. The International Prognostic Index (IPI) assigns 1 point for each factor to the total score and categorises patients into 4 groups based on the total score: 0/1 = low risk, 2 = low-intermediate risk, 3 = high-intermediate risk, and 4/5 = high risk.

The presence of B symptoms, bulky disease (i.e. tumour diameter ≥7.5 cm or ≥10 cm), elevated serum β2-microglobulin level, low haemoglobin and serum albumin levels, and bone marrow involvement have also been identified as prognostic factors.

Current treatment options

Most patients with DLBCL are cured with initial treatment using rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP).[9] However, about 10% of patients do not respond adequately to initial treatment (primary refractory disease), and nearly one-third of patients will later relapse after achieving a complete response (CR). Prognosis and treatment vary according to whether disease was refractory to initial systemic therapy and with the interval from initial treatment until relapse. Management is influenced by whether the patient has primary refractory disease, first relapse, or second or later relapse; prior treatment(s) and the response to those treatment(s), plus the level of medical fitness.

For patient whose relapse occurs > 12 months, haematopoietic stem cell transplantation (HSCT) may be an option. For patients who are not proceeding to HSCT, the options are clinical trial, a

[7] Swerlow SH, et al., The 2016 revision of the World Health Organization classification of lymphoid neoplasms, Blood, 2016, 127(20): 2375-2390

[8] Nowakowski GS, *et al.,* 2015

[9] An alternative treatment regimen of rituximab plus cyclophosphamide, doxorubicin, polatuzumab vedotin, and prednisone is approved in Australia.

second line therapy, palliative ISRT of best supportive care. Second line therapy options[10] for patients ineligible for autologous HSCT include other combination treatment regimens such as the combination of polatuzumab vedotin + bendamustine + rituximab, tafasitamab + lenalidomide, or rituximab-based combination chemotherapy regimens.

For patients whose relapse occurs <12 months from primary treatment or who have primary refractory disease second line therapy may include Chimeric Antigen Receptor (CAR) T-cell therapy or one of the second-line treatment regimens mentioned in the previous paragraph.

Overall Response Rates (ORRs) of 52% to 83% have been reported for CAR-T-cell therapies[11] but many patients are ineligible due to serious comorbidities and/or where rapidly progressing disease make the wait times required for patient-specific CAR T-cell manufacturing prohibitive. Other limitations include toxicity with the need for intense monitoring, and restricted availability which currently limits the use of CAR T-cell therapies to specialised tertiary centres. In addition, early relapse has been shown to occur in patients CAR T-cell therapy, with reported rates of the order of approximately 35% – 47% in independent accounts.

There are limited effective therapeutic options for patients with R/R DLBCL who have received two or more lines of systemic therapy. Treatments suggested by the NCCN Clinical Practice Guidelines in this setting include chimeric antigen receptor T-cells and bi-specific T cell engagers, in additional to the trial of older regimens if not already used in earlier lines of treatment.

Two CAR T-cells, axicabtagene ciloleucel (YESCARTA) and tisagenlecleucel (KYMRIAH), are currently approved in Australia for patients with R/R DLBCL who have received two or more lines of systemic therapy. BREVANZI, isoantigenic maraleucel, is also approved internationally with indications that include treatment of adult patients with R/R DLBCL after two or more lines of systemic therapy.

Bispecific T-cell engagers include glotifamab and epcoritamab. Glofitamab (COLUMVI) is a bispecific MAb that was provisionally approved in August 2023 and is indicated for:

> *COLUMVI monotherapy with obinutuzumab pretreatment has provisional approval for the treatment of adult patients with relapsed or refractory DLBCL after two or more lines of systemic therapy. COLUMVI is not indicated for the treatment of patients with primary central nervous system lymphoma.*

Clinical rationale

Epcoritamab is a bispecific antibody that recognises the T-cell antigen CD3 and the B-cell antigen CD20 and triggers T-cell-mediated killing of CD20-expressing 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 It binds bivalently (with high avidity) to CD20 expressed on the surface of B cells and monovalently to CD3 in the T-cell receptor complex expressed on the surface of T cells.

Epcoritamab acts by the engagement of T cells as effector cells to induce killing of CD20-expressing B cells and tumour 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. This

[10] National Comprehensive Cancer Network Guidelines Version 6.2023 Diffuse Large B-cell Lymphoma

[11] Westin J, Sehn LH CAR T cells as a second-line therapy for large B-cell lymphoma: a paradigm shift? Blood 2022; 139(18):2737-2746

mechanism of action is in contrast to chemotherapy, or conventional CD20-targeting monoclonal antibodies such as rituximab that induce cytotoxicity through Fc-mediated effector functions such as antibody-dependent cellular cytotoxicity, antibody-dependent cell-mediated phagocytosis and complement-dependent cytotoxicity, and in some cases programmed cell death.

Because CD20-specific mAbs are part of the standard of care for the treatment of B-cell malignancies, many patients will have received prior treatment with these mAbs. Resistance to CD20-targeting agents is rarely caused by loss of CD20 expression as evidenced by the presence of CD20 on B cells in most patients previously treated with CD20 antibody containing regimens. Therefore, a CD20-targeting antibody with a different mechanism of action compared to CD20-specific mAbs may provide a new strategy to treat CD20-expressing B-cell malignancies, such as DLBCL.

Regulatory status

Australian regulatory status

This product is considered a new biological entity for Australian regulatory purposes. On 10 January 2023 epcoritamab was granted provisional determination for the treatment of adult patients with relapsed or refractory DLBCL after 2 or more lines of systemic therapy and orphan drug designation for the treatment of patients with DLBCL.

International regulatory status

On May 19, 2023, the FDA granted accelerated approval to epcoritamab with the following indication:

> *EPKINLY is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), not otherwise specified, including DLBCL arising from indolent lymphoma, and high-grade B-cell lymphoma after two or more lines of systemic therapy. This indication is approved under accelerated approval based on response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).*

Epcoritamab also granted conditional approval in Canada on 13 October 2023 for the following indication:

> *EPKINLY, is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL - not otherwise specified, DLBCL transformed from indolent lymphoma, high grade B-cell lymphoma (HGBCL), primary mediastinal B-cell lymphoma or follicular lymphoma Grade 3B (FLG3b) after two or more lines of systemic therapy and who have previously received or are unable to receive CAR T-cell therapy.*
> *EPKINLY has been issued marketing authorization with conditions, pending the results of trials to verify its clinical benefit. Patients should be advised of the nature of the authorization.*

Epcoritamab, with the trade name TEPKINLY has conditional authorisation in the EU for the following indication:

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

Registration timeline

This submission was evaluated under the provisional registration process and the active ingredient with its proposed indication was given orphan drug designation.

Table 1 captures the key steps and dates for this submission

Table 1. Registration timeline for EPKINLY (epcoritamab), submission PM-2023-00662-1-6

Description	Date
Designation (Orphan)	10 January 2023
Determination (Provisional)	10 January 2023
Submission dossier accepted and evaluation commenced	4 April 2023
Evaluation completed	29 November 2023
Registration decision (**Approved**)	19 February 2024
Registration in the ARTG completed	6 January 2025
Number of working days from submission dossier acceptance to registration decision*	222 days

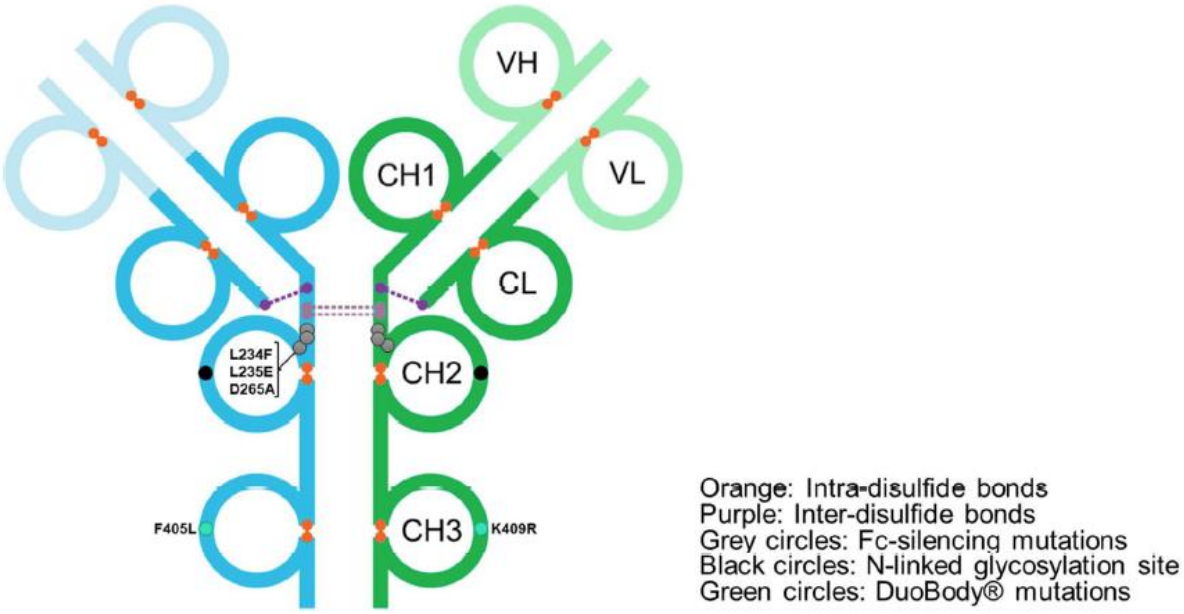
*The provisional registration process has a target timeframe of 220 working days.

Assessment overview

Quality evaluation summary

Epcoritamab is a glycoprotein belonging to the immunoglobulin (Ig) superfamily, composed of two heavy chains and two light chains. The heavy chains belong to the gamma (γ) isotype, form 1 (G1), and the light chains to the kappa (κ) and lambda (λ) type, making epcoritamab a bispecific IgG1λκ antibody. The structure of epcoritamab is shown in Figure 1.

Figure 1. Structure of epcoritamab



The two heavy chains are bound to each other by two interchain disulfide bonds, and one light chain is bound to one heavy chain by a single interchain disulfide bond. Each light chain has two intrachain disulfide bonds, and each heavy chain has four intrachain disulfide bonds.

The amino acid sequences for the heavy and light chain from parental antibodies (3001d in green and 3005a in blue in the schematic Figure 1 above) have been provided. The theoretical molecular weight of epcoritamab is 148,535 Da.

The active pharmaceutical ingredient epcoritamab (DuoBody-CD3xCD20; GEN3013, ABBV-GMAB-3013) is manufactured from two antibody intermediates by DuoBody technology. The two parental antibodies 3001d and 3005a are produced in Chinese hamster ovary (CHO) cells, each contain a matched point mutation (F405L and K409R, respectively), facilitating the formation of the DuoBody molecule, epcoritamab.

Epcoritamab generated using the DuoBody technology by a process called controlled Fab-arm exchange. All steps are performed at ambient temperature (18 °C to 25 °C), unless specified otherwise. All filtration membranes are single use.

The overall quality of the active substance was demonstrated via adequate control of the starting materials, control of critical steps and intermediates, process validation, extensive characterisation using orthogonal and state-of-the-art analytical methods, control of impurities and contaminants, generation of robust reference materials and batch analyses that covered multiple manufacturing campaigns.

The quality controls testing for epcoritamab includes appearance (Ph. Eur.), pH (Ph. Eur.), purity, identity, quantity, potency, process-related impurities and endotoxins/bioburden (Ph. Eur.)

The biological activity is tested using a T-cell activation bioassay. The proposed release specification for the active substance is found acceptable, with respect to test methods chosen. The proposed specification limits are based on batch analyses and stability study results. This approach is considered acceptable.

Stability data have been generated under real time and stressed conditions to characterise the stability profile of the active ingredient and to establish a shelf life. The real time data submitted

support a shelf life of 30 months when stored at ≤ - 60°C. The drug substance is not photostable and needs to be protected from light.

Epcoritamab finished product EPKINLY is a sterile, preservative-free liquid supplied in a single dose 2 ml glass vial, with a fluoropolymer-coated rubber stopper and an aluminium cap with flip-off top. The epcoritamab drug substance is formulated as an isotonic aqueous solution in a buffer containing 30 mM acetate, 150 mM sorbitol, 0.04% polysorbate 80, pH 5.5. The formulation development has been adequately described and the final formulation intended for marketing was used in the phase III clinical trials.

There are no novel excipients. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur/USP-NF/JP standards.

The container closure is considered suitable for its intended use as demonstrated by compatibility and stability studies.

The description of the manufacturing process has been provided in sufficient detail.

All analytical methods used for testing of the finished product were described to the satisfaction of the Evaluator.

The reference standard used in the testing and release of epcoritamab finished product is the same as the one used for the testing and release of epcoritamab active substance.

The quality control of finished product for batch release is described and found acceptable.

Stability data have been generated under stressed and real time conditions to characterise the stability profile of the product. Following evaluation, the recommended storage condition is 2 years when stored at 2-8°C.

In-use study results demonstrate appropriate in-use stability and compatibility of epcoritamab drug product for the proposed conditions of use for not more than 24 hours at 2-8 °C, including 12 hours at room temperature from the start of dose preparation to the start of administration.

The product is not photostable. Secondary packing is adequate for protection against light.

The Evaluator recommends approval from a quality perspective.

Nonclinical evaluation summary

The nonclinical Evaluator raised no nonclinical objections to the provisional registration of EPKINLY for the proposed indication.

The nonclinical data contained an adequate set of studies, consistent with relevant guidelines for the nonclinical assessment of anticancer and biotechnology-derived pharmaceuticals (ICH S9 and ICH S6 [R1]).[12] The overall quality of the nonclinical dossier was high. Pivotal safety-related studies were Good laboratory Practice (GLP)-compliant.

Epcoritamab is a recombinant bispecific IgG1 monoclonal antibody directed against human CD20 and human CD3. Epcoritamab is intended to simultaneously bind to CD20 (expressed on the surface of target B cells) and CD3 (expressed on effector T cells) to cause T cell activation and target cell lysis.

In vitro, epcoritamab was shown to bind to human CD20 and CD3 with nanomolar affinity, and to induce T cell activation and T-cell-mediated cytotoxicity in the presence of CD20-expressing

[12]International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH S6 (R1) Preclinical safety evaluation of biotechnology-derived pharmaceuticals - Scientific guideline. June 201.

target cells. Epcoritamab displayed picomolar cytotoxic potency against all human B-cell lymphoma cell lines tested, as well as primary malignant B cells obtained from newly diagnosed or relapsed/refractory patients with DLBCL. Anti-tumour activity was demonstrated in vivo in humanised mice bearing human B-cell lymphoma cell lines and patient-derived DLBCL cells. These primary pharmacology studies offer support for the utility of epcoritamab for the proposed indication.

Normal B cells are also targeted by epcoritamab.

Epcoritamab recognises the cynomolgus monkey forms of CD20 and CD3 with comparable affinity cf. human. Epcoritamab is not pharmacologically active in other routine laboratory animal species.

Immunohistochemical experiments involving a suitably comprehensive set on human and cynomolgus monkey tissues revealed no off target binding for epcoritamab, with the staining pattern consistent with the known expression pattern of CD20 and CD3 and the expected tissue distribution of B and T lymphocytes.

Mutations introduced into the Fc region of epcoritamab silence effector function such as antibody-dependent cellular cytotoxicity (ADCC), complement-dependent cellular cytotoxicity (CDC), and antibody-dependent cellular phagocytosis.

The pharmacokinetic profile of epcoritamab in cynomolgus monkeys was characterised by slow absorption and high bioavailability after SC administration, and greater than dose-proportional exposure (indicative of target-mediated drug disposition). The plasma half-life of epcoritamab is shorter in cynomolgus monkeys cf. humans (~3–4 days cf. ~22–24 days), but this does not have a critical impact on the use of this animal model to investigate the toxicity of epcoritamab.

Single- and repeat-dose toxicity studies were performed in cynomolgus monkeys. SC and IV routes of administration were used. The pivotal repeat-dose toxicity study was of 5 weeks duration. While short, this is acceptable, with longer studies not feasible due to the development of anti-drug antibodies that resulted in loss of exposure. The development of anti-drug antibodies to humanised protein in monkeys is not predictive of immunogenicity in patients.

No effects on cardiovascular or respiratory function, and no direct neurological effects, were seen with epcoritamab in monkeys.

The major findings in the toxicity studies are attributable to the drug's primary pharmacology, and comprised B-cell depletion, decreased lymphoid cellularity in lymphoid tissues, cytokine release (resulting in adverse clinical signs), and various haematological changes. Effects were reversible.

Epcoritamab was well tolerated locally in monkeys by the SC and IV routes.

No genotoxicity or carcinogenicity studies were conducted, in line with ICH guidelines.

The Evaluator supported Pregnancy Category C. No reproductive and developmental toxicity studies were performed with epcoritamab, with the potential for adverse effects on embryofetal development assessable from the class/mechanism of action. Placental transfer is expected for an IgG antibody. The key risk is seen to be pharmacologically mediated fetal B-cell depletion. Epcoritamab-induced cytokine release may also pose a risk for embryofetal loss.

Clinical evaluation summary

Pharmacology

Epcoritamab is proposed for subcutaneous (SC) injection only according to the schedule in Table 2.

Table 2. Epcoritamab dosing schedule

Cycle	Cycle 1				Cycles 2 & 3				Cycles 4-9				Cycles 10+			
Day of Cycle	1	8	15	22	1	8	15	22	1	8	15	22	1	8	15	22
EPKINLY (mg)	0.16[a]	0.8[b]	48	48	48	48	48	48	48	-	48	-	48	-	-	-
[a]0.16 mg is a priming dose [b]0.8 mg is an intermediate dose																

The dosing schedule includes an initial priming dose of 0.16 mg on Cycle 1 Day 1, an intermediate dose of 0.8 mg on Cycle 1 Day 8, and a full dose of 48 mg administered from Cycle 1 Day 15 and onwards. Dosing is to continue until disease progression or unacceptable toxicity.

Pharmacokinetics

Two ongoing studies provided data to support the use of epcoritamab monotherapy in R/R large B-cell lymphoma (LBCL), including DLBCL. Study GCT3013-01, a Phase 1/ 2 study includes a dose escalation (ESC) part and an expansion (EXP) part with aggressive B-cell non-Hodgkin lymphoma (aNHL) (i.e., patients with LBCL), indolent B-cell non-Hodgkin lymphoma (iNHL), and mantle cell lymphoma (MCL) cohorts, and study GCT3013-04, a supportive Japanese phase 1/2 study includes a ESC part and an EXP part with DLBCL and follicular lymphoma (FL) cohorts. Pharmacokinetic results were predominantly from popPK report using data from these studies. Results from the individual studies are shown in section 19.1 of the CER.

Population PK data (popPK)

Epcoritamab is to be administered by SC injection. Following SC administration of the proposed full dose of epcoritamab (i.e., 48 mg) to a mixed population of patients with iNHL and aNHL.

The PK of epcoritamab was described using a two-compartment target mediated drug distribution (TMDD) model with first-order SC absorption.

The time to maximum concentration (T_{max}) was approximately 92.9 h. The popPK derived estimate of the absorption rate (K_a) for epcoritamab was 0.584 day-1. At steady state of the once every 4 weekly dosing period (Q4W) compared to C1D15, the predicted accumulation ratios for geometric mean C_{max} were 3.96 and 3.55, respectively. Modelling indicated that epcoritamab concentrations appeared to approach or reach steady-state by approximately 3 months after the start of each dosing interval (QW, Q2W, or Q4W).

The popPK estimate for the geometric mean central volume of distribution (Vc/F) in patients with R/R DLBCL enrolled in Study GCT3013-01 was 8.27 L. No studies have directly investigated the metabolic pathways involved in the breakdown of epcoritamab. However, like other antibodies it is expected that epcoritamab is not primarily cleared via hepatic or renal pathways; instead, the primary elimination pathways are presumed to be protein catabolism.

Dose-dependent TMDD saturation was predicted to be observed on both Days 21 and 84 after QW dosing with 48mg and 60mg.

The primary elimination pathways of epcoritamab are protein catabolism. The popPK predicted estimate of epcoritamab geometric mean clearance (CL/F) in patients with R/R DLBCL enrolled

in Study GCT3013-01 following a 48 mg dose is 0.441L. Following dosing with 48 mg QW the predicted washout time was approximately 110 days, corresponding to washout half-life of 22 days if dosing stopped at Week 12. If dosing stopped at the end of Q2W (Week 36) or steady-state of the Q4W (Week 60) dosing period the predicted washout times were 122 days and 111 days, respectively, approximately corresponding to washout half-lives of 24.4 days and 22.2 days, respectively.

Estimates of inter-individual variability (IIV) were low for epcoritamab CL/F (coefficient of variation [CV]=25.7%) and Vc/F (CV=31.2%) but were high for all other parameters (CV 55 to 138%). Intra-individual (residual) variability was low (CV=18.9%) and the IIV on the magnitude of the intra-individual (residual) error was estimated to be 21.2%.

Body weight was significant covariate on epcoritamab CL/F. Epcoritamab exposures levels were lower in patients with higher body weight and higher in patients with lower body weight, though the predicted differences in CL/F and Vc/F for the extreme values of weight (44.7 kg and 110 kg, defined as 2.5th and 97.5th percentiles of weight distribution in the analysis population) were less than 39.8% and 26.8%, respectively, compared to an individual of typical weight (75 kg). Age, sex, laboratory values, renal and hepatic function, ECOG score, and tumour size had no meaningful effects on epcoritamab exposures.

Pharmacodynamics

Epcoritamab 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 leukaemia's and on B cells in peripheral blood, but not haematopoietic stem cells or plasma cells. Epcoritamab does not have direct immune effector mechanisms. Its activity is dependent upon simultaneous engagement of CD20-expressing cancer cells and CD3-expressing endogenous T cells that induce specific T-cell activation and T-cell-mediated killing of CD20-expressing cells.

No significant association between epcoritamab concentrations and ΔQTcF was observed in patients with LBCL or DLBCL (p values = ~0.71). At the arithmetic mean predicted Cmax of 11.7 µg/mL, predicted QTcF prolongation was -0.06 msec (upper bound of one-sided 95% CI 4.23 msec).

There were no apparent exposure – response (E-R) relationships between exposure and: ≥ grade 3 treatment emergent adverse events (TEAEs), ≥ grade 3 neutropenia (TEAE), ≥ grade 3 TEAE of infections, or injection site reactions, serious adverse events (SAEs), TEAEs leading to dose delay or dose discontinuation, all grades of cytokine release syndrome (CRS), ≥ grade 2 CRS, CRS requiring tocilizumab, immune effector cell-associated neurotoxicity syndrome (ICANS), and clinical tumour lysis syndrome (CTLS).

Immunogenicity

Across all dose levels, 14 (4.3%) of 327 PK-evaluable patients were antidrug antibody (ADA) - positive, and of the ADA-positive patients four (1.2%) had a titre ≥1:80 (after accounting for dilutions). Among the 300 PK-evaluable patients who received the full dose of 48 mg 10 (3.3%) were ADA-positive.

In Study GCT3013-01, 4 /158 (2.5%) ADA-evaluable patients with LBCL who received epcoritamab at the proposed dosing regimen became ADA positive on treatment, all with low titres. Due to the low numbers no meaningful analysis of the effect of antibody positivity on safety or efficacy could be performed.

There were no meaningful differences in epcoritamab PK between ADA-negative and ADA-positive patients after adjusting for other covariates.

Efficacy

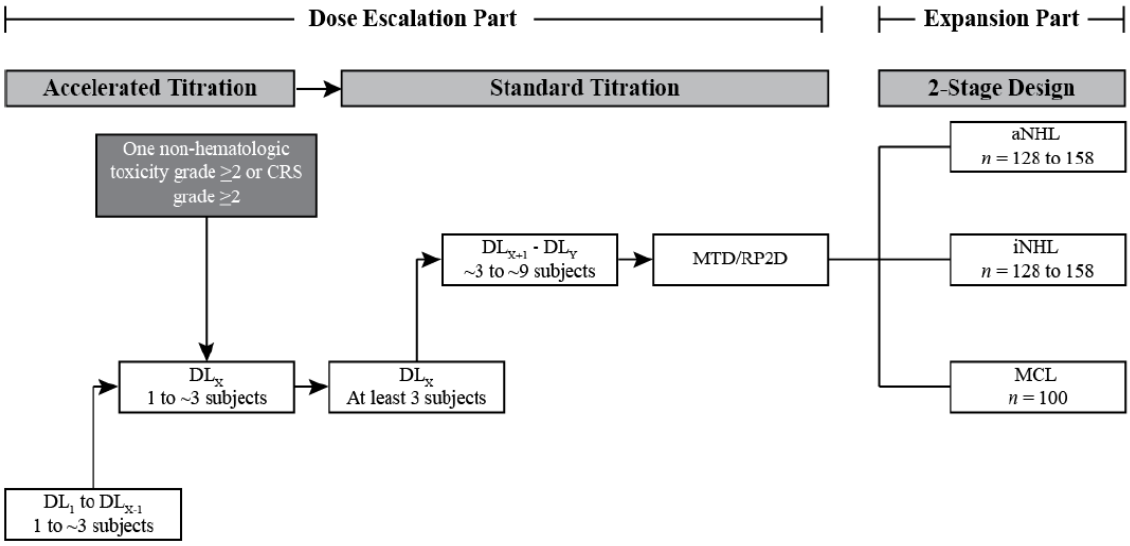
Study GCT3013-01

Study GCT3013-01 was a multicentre, multinational, Phase 1/2, open-label, first-in-human, ESC/EXP trial of epcoritamab in patients with relapsed, progressive or refractory B-cell lymphoma.

The study included an ESC part and an EXP part as shown in Fig. 2. The ESC, conducted in sites in Western Europe and the United Kingdom, commenced in in June 2018 and is ongoing. The EXP part, conducted in sites in Europe, North America and Australia commenced in June 2020, and is also ongoing.

The epcoritamab recommended Phase 2 dose (RP2D) regimen was selected based upon results from the ESC of the trial and consisted of an initial priming dose of 0.16 mg (Cycle 1 Day 1 [C1D1]), an intermediate dose of 0.8 mg (C1D8), and a full dose of 48 mg at C1D15, C1D22, and thereafter (Figure 2).

Figure 2. Overview of GCT3013-01 Trial Design



aNHL = aggressive non-Hodgkin lymphoma subtypes: CRS = cytokine release syndrome; DL dose level: iNHL = indolent non-Hodgkin lymphoma subtypes; MCL mantle cell lymphoma: MID - maximum tolerated dose; RP2D = recommended phase 2 dose: X = the dose level where the bigger (grade 2 non-hematological toxicity etc.) is observed: switch from single subject cohort to 3 subject cohort; Y = the highest investigated dose level.

Dose escalation part - Dose-finding

The SC route of administration was chosen for epcoritamab based on its lower Cmax value and lower peak cytokine levels, but comparable B-cell depletion compared to IV administration at the same doses (mg/kg) in the nonclinical studies.

The ESC Part informed the recommended Phase 2 epcoritamab dose regimen (EXP of study GCT3013-01) of a 0.16 mg priming dose on cycle 1 day 1 [C1D1], 0.8 mg intermediate dose on C1D8, and 48 mg full dose on C1D15, C1D22, and thereafter) all via subcutaneous injection, was selected based on data from the ESC Part of that study, in combination with population-PK modelling, PK/pharmacodynamic modelling, exposure-response analysis, and exposure-AE analysis.

The proposed epcoritamab priming (0.16 mg) and intermediate (0.8 mg) doses were selected with the aim of reducing the incidence of cytokine release syndrome (CRS). The proposed priming and intermediate doses had similar or numerically lower incidence of CRS (any grade)

during Days 1 to 8 and Days 8 to 15, respectively, compared to the other regimens studied in the ESC of study GCT3013-01.

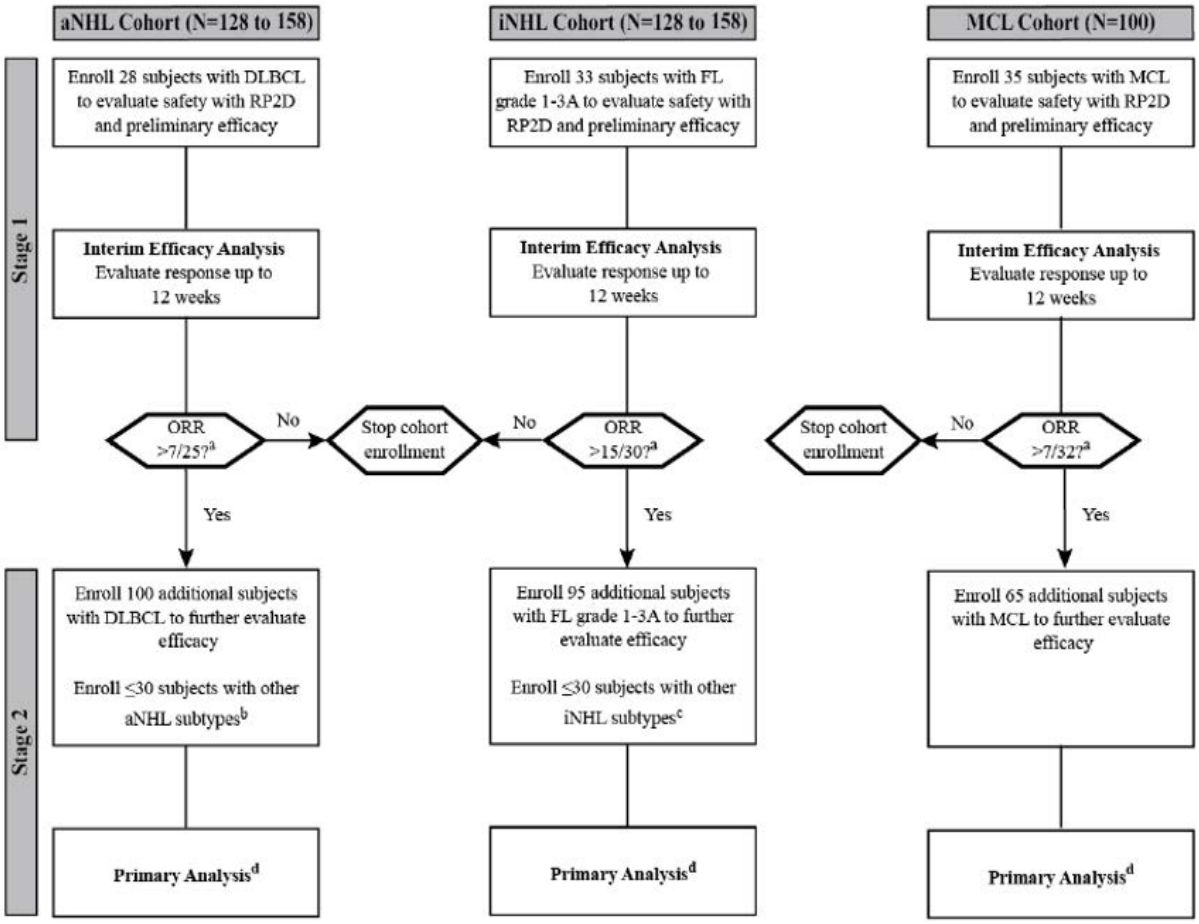
Expansion part

In the EXP of the trial, epcoritamab was administered as monotherapy by subcutaneous (SC) injection once weekly (QW) during Cycles 1 to 3, once every 2 weeks (Q2W) during Cycles 4 to 9, and once every 4 weeks (Q4W) during Cycle 10 and beyond (until unacceptable toxicity, progressive disease [PD], or withdrawal of consent). No dose reduction of epcoritamab on an individual subject level was allowed.

The EXP of the trial was initiated with parallel enrolment in three cohorts of patients who were treated with the RP2D regimen of epcoritamab (Figure 3). The EXP consisted of three disease cohorts: patients with aNHL (also referred to as LBCL), indolent B-cell Non-Hodgkin lymphoma (iNHL), and mantle cell lymphoma (MCL).

The submitted interim clinical study report (CSR) reported efficacy data from the aNHL cohort of the EXP of the trial only (enrolment completed).

Figure 3. GCT3013-01 Expansion Scheme



aNHL = aggressive B-cell non-Hodgkin lymphoma; DLBCL = diffuse large B-cell lymphoma: FL = follicular lymphoma: iNHL = indolent non-Hodgkin lymphoma: MCL = mantle cell lymphoma: ORR = overall response rate: RP2D = recommended phase 2 dose. a. For the interim analysis, response was determined by Lugano criteria and assessed by the investigator and Sponsor based on available data (eg, efficacy, safety, pharmacodynamics, biomarkers). The denominator for the interim analysis accounted for a 10% dropout rate. b. Other LBCL subtypes include high grade B-cell lymphoma, primary mediastinal B-cell lymphoma, and FL

grade 3B. c. Other iNHL subtypes include marginal zone lymphoma and small lymphocytic lymphoma. d. For primary analysis, response was determined by Lugano criteria and assessed by IRC.

Patients enrolled in the aNHL expansion cohort were aged 18 years or older with an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2, and had documented evidence of CD20+ mature B-cell neoplasm according to World Health Organization (WHO) classification 2016 or WHO classification 2008 based on representative pathology report. Patients must have had measurable disease, defined as a computed tomography (CT)/magnetic resonance imaging (MRI) scan with at least 1 measurable lesion and a fluorodeoxyglucose (FDG)-positron emission tomography (PET) scan that demonstrated positive lesion(s) (for FDG-avid lymphomas only).

Patients must have been diagnosed with DLBCL (de novo or transformed from all indolent subtypes including Richter's transformation), including patients diagnosed with double-hit (DH) or triple-hit (TH) DLBCL, with MYC and BCL2 and/or BCL6 rearrangements, or other LBCL subtypes (including PMBCL, HGBCL, or FL3B).

Patients must have had relapsed or refractory disease and previously been treated with at least 2 lines of systemic antineoplastic therapy, including at least 1 anti-CD20 monoclonal antibody-containing therapy. Patients 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.

Patients were excluded from the EXP of the trial if they had primary central nervous system (CNS) lymphoma or known CNS involvement, past or current malignancy (except for those noted in the protocol), aspartate transaminase (AST) or alanine transaminase (ALT) >3 × upper limit of normal (ULN), total bilirubin >1.5 × ULN (unless bilirubin rise is due to Gilbert's syndrome or of non-hepatic origin), creatinine clearance <45 mL/min, clinically significant cardiac disease, chronic ongoing infectious diseases, diseases or treatments resulting in immunosuppression, or seizure disorders requiring therapy.

Baseline demographics in the R/R DLBCL population

The patients with R/R DLBCL are the most relevant for the requested indication. Most DLBCL patients were White (60.4%) and male (61.2%), with a median age of 66.0 years.

Most (69.8%) had de novo disease, 28.8% had transformed disease, and 1.4% had unknown DLBCL type. Most (61.9%) had Stage IV disease by the Ann Arbor classification, and 59.0% had an IPI ≥3. Most (59.0%) had primary refractory disease, and 74.8% were refractory to ≥2 consecutive lines of prior anti-lymphoma therapy.

The median number of prior lines of anti-lymphoma therapy was 3.0 (range: 2, 11), with 33.8% having received 3 prior lines of therapy and 36.7% having received ≥4 prior lines of therapy. Prior therapies included anti-CD20 therapy (100%), alkylating agents (100%), anthracyclines (98.6%), a nucleotide (82.7%), topoisomerase inhibitor (66.9%), polatuzumab vedotin (9.4%), autologous stem cell transplant (18.7%), and CAR T-cell therapy (38.1%). The median time from the end of the last-line anti-lymphoma therapy to the first dose of epcoritamab was 2.5 months.

Participant flow in the R/R DLBCL population

As of the data cut-off (DCO) date of 31 Jan 2022, a total of 219 patients were screened and 157 patients received at least one dose of epcoritamab in the aNHL expansion cohort. Of those, 139 patients had DLBCL, and 18 patients had other LBCL subtypes (9 patients with HGBCL, 5 patients with FL grade 3B, and 4 patients with PMBCL). Forty-seven (33.8%) patients with R/R DLBCL were continuing epcoritamab treatment at the time of the data cut-off.

In R/R DLBCL patients, the median number of cycles initiated was 5.0 (range: 1, 20) and the median duration of treatment was 4.1 months (range: 0, 18), and the median duration of follow-up was 11.0 (range: 0.3+, 17.9) months.

Among the 92 (66.2%) patients who discontinued epcoritamab treatment, the most frequent primary reasons were: disease progression (51.8%), adverse events (7.9%), and the decision to proceed with transplant (3.6%). Sixty three patients (45.3%) permanently discontinued the trial, mostly as a result of the patient's death (38.1%).

Forty eight patients (34.5%) received a subsequent anti-lymphoma treatment after discontinuing epcoritamab. Most (37 patients) received a systemic drug therapy regimen, but 14 patients received radiotherapy, 7 patients received CAR T therapy, and 6 patients received a stem cell transplant.

Protocol amendments and protocol deviations

There were 7 protocol amendments. The final protocol amendment in September 2020 added, inter alia, the MCL cohort, clarification that double hit or triple hit DLBCL would include patients with MYC and BCL2 and/or BCL6 translocations only and added Duration of Complete Response (DOCR) as a secondary endpoint.

The Evaluator noted that at least one major protocol deviation occurred in 6 patients in the R/R DLBCL cohort but did not consider these would have a meaningful impact on the study conclusions.

Study endpoints

The primary endpoint was ORR determined by Lugano criteria as assessed by the Independent Review Committee (IRC). ORR was defined as the proportion of patients whose best overall response was a CR or partial response (PR). Imaging was obtained during the treatment period every 6 weeks for the first 24 weeks, every 12 weeks until week 48, and every 6 months thereafter until disease progression. Secondary endpoints, as determined by Lugano criteria per IRC assessment, included duration of response (DOR), CR, DOCR, progression-free survival (PFS) and time to response (TTR). Rate of minimal residual disease (MRD) negativity was also secondary endpoint.

No formal hypothesis testing was performed on the aNHL expansion cohort. Analyses of trial participants and efficacy were performed using the Full Analysis Set (FAS), defined as all patients who had been exposed to epcoritamab.

Treatments

The epcoritamab dose regimen in Study GCT3013-01 is shown in Table 3. Treatment beyond cycle 10 occurred until unacceptable toxicity, progressive disease or withdrawal of consent.

Table 3. Study GCT3013-01 dose regimen

Cycle	Cycle 1				Cycles 2 & 3				Cycles 4-9				Cycles 10+			
Day of Cycle	1	8	15	22	1	8	15	22	1	8	15	22	1	8	15	22
EPKINLY (mg)	0.16[a]	0.8[b]	48	48	48	48	48	48	48	-	48	-	48	-	-	-

[a]0.16 mg is a priming dose
[b]0.8 mg is an intermediate dose

Patients also received pre-medication with corticosteroids (prednisolone 100 mg IV or equivalent, including oral dose), antihistamines (diphenhydramine 50 mg IV or oral or equivalent), and antipyretics (paracetamol 650 to 1000 mg PO or equivalent) 30 to 120 minutes

prior to each of the first 4 doses of epcoritamab (Cycle 1). For subsequent doses of epcoritamab, premedication and CRS prophylaxis were optional.

Corticosteroid dosing was also given on Days 2, 3 and 4 of epcoritamab dosing in Cycle 1, and if re-priming epcoritamab dosing was needed after a treatment interruption. Based on the investigator's evaluation, the corticosteroid daily dose requirement could be reduced to mitigate possible adverse effects from high-dose steroid administration.

If CRS ≥ grade 2 occurred following the fourth epcoritamab dose the same 4-day corticosteroid regimen was given. The regimen was repeated with each subsequent epcoritamab dose until a dose was given after which no CRS occurred.

Hospitalisation was required for a minimum of 24 hours after the first full dose of epcoritamab in Cycle 1.

The treatment period continued until disease progression unless the patient fulfilled one of the discontinuation criteria. The trial will run for a maximum of 5 years after the last patient's first dose.

Results

The Sponsor's requested indication is limited to R/R DLBCL, consistent with the provisional determination indication. The relevant efficacy data from the DLBCL patient population of Study GCT3013-01 are presented in this section.

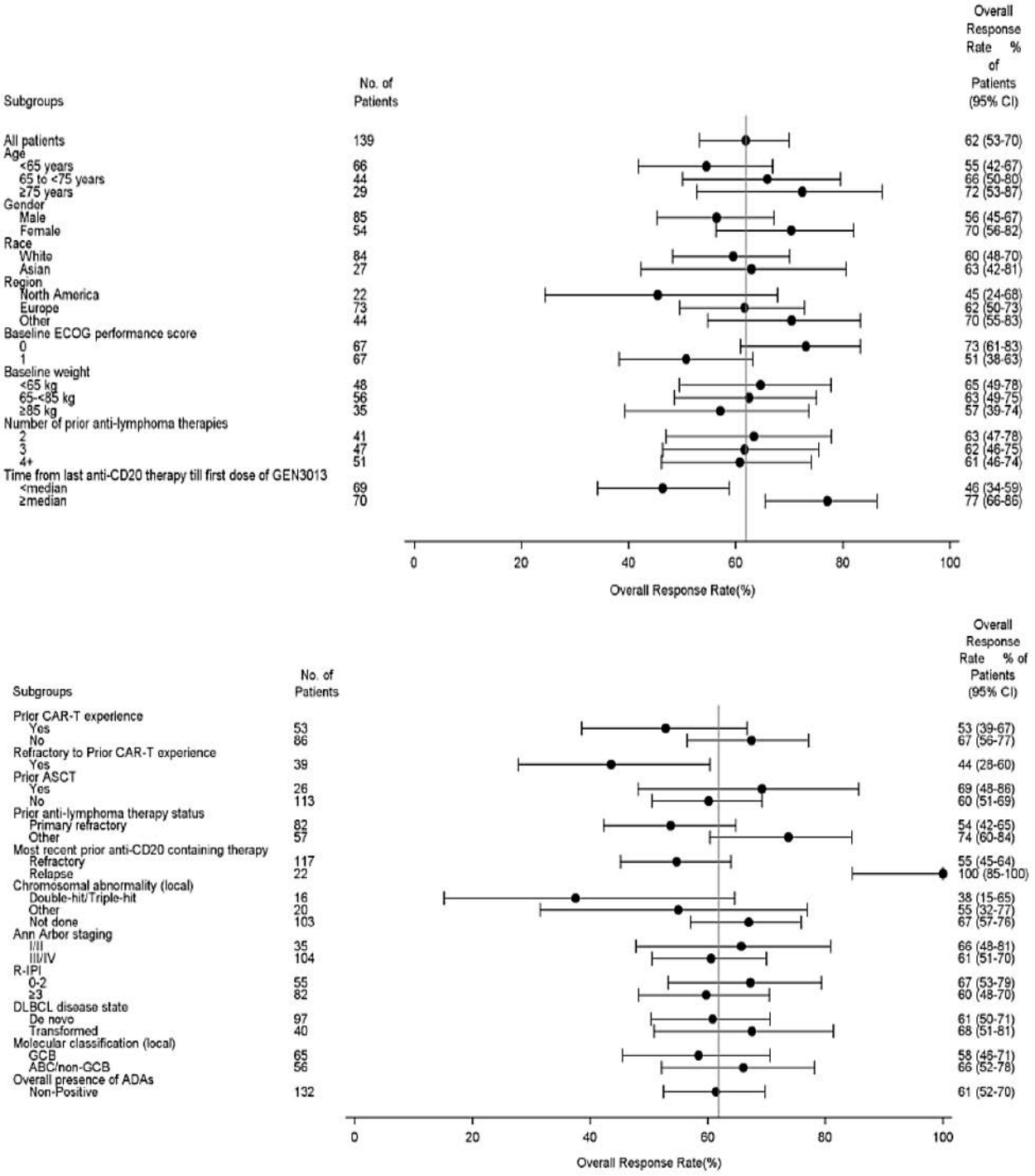
The results for the primary endpoint at the 31 January 2022 DCO were:

ORR, n (%) (95% CI): 86 (61.9%) (53.3, 70.0)

- CR, n (%)(95% CI): 54 (38.8%)(30.7, 47.5)
- Best overall response
  - CR, n (%): 54 (38.8%)
  - PR, n (%): 32 (23.0%)
  - Stable disease (SD), n (%): 4 (2.9%)
  - Progressive disease (PD), n (%): 33 (23.7%)
  - Not evaluable (NE), n (%): 16 (11.5%)

Subgroup analysis of ORR across a variety of pre-specified subpopulations are shown Figure 4.

Figure 4. Forest Plot of Overall Response in Prespecified Subgroups Based on IRC Assessment Determined by Lugano Criteria – LBCL Expansion Part (Full Analysis Set; GCT3013-01), DLBCL Patients.



Abbreviations: ADA = anti-drug antibody. aNHL = aggressive B-cell non-Hodgkin lymphoma: ASC7 = autologous stem cell transplantation: CAR T = Chimeric antigen receptor T-cell: CI = confidence interval: DLBCL= diffuse large B-cell lymphoma: ECOG = Eastern Cooperative Oncology Group: GCB = germinal centre B-cell: IHC = immunohistochemistry: IPI = International Prognostic Index. Note: Results of response in subgroups by local laboratory analysis of chromosomal abnormality are not discussed due to availability of data from a more robust retrospective central analysis by FISH. Data cutoff date: 31 Jan 2022.

In patients who achieved PR or CR (n=86), the median DOR was 12.0 months (95% CI: 6.6, NR). The estimated percentage of patients remaining in response at 3, 6, and 9 months was 75.8%, 63.3%, and 61.6%, respectively.

In patients who achieved CR the median DOCR (per IRC) was 12.0 months (95% CI: 9.7, NR). The estimated percentage of patients remaining in CR at 3, 6, and 9 months was 95.7%, 85.3%, and 85.3%, respectively.

Only 55 patients contributed MRD results. Analyses were conducted using 10-4, 10-5 and 10-6 cut-offs. At the MRD cut-off of 10-5, MRD negativity was reported in 68.1% (95% CI: 52.9%, 80.9%). The analysis of MRD did not correlate sufficiently with clinical response and a high rate of patients with PD were considered MRD negative. In an exploratory analysis by ctDNA assay MRD negativity (n=94) was reported in 46.8% (95% CI: 36.4, 57.4). Median duration of MRD negativity was not reached, and an estimated 78.7% of patients (95% CI: 61.3, 88.9) were remaining in MRD negativity at 6 months.

PFS, Overall Survival and Time to Next Anti-lymphoma Therapy were assessed however given this was an open label, non-comparative study these parameters are not interpretable. Improvements in the patient-reported symptoms were observed while on treatment across all 6 symptoms (body pain, fever, night sweats, lack of energy, tires easily, and weight loss) from C2D1 to C13D1, however these findings are from an open-label, non-comparative study and may be subject to bias.

Study GCT3013-04 is an ongoing multicentre, Phase 1/2, open-label, ESC/EXP study conducted to assess the safety and preliminary efficacy of epcoritamab in Japanese patients with R/R B-cell non-Hodgkin lymphoma (B-NHL). The study had two parts: ESC and an EXP part comprising a Monotherapy Part and a Combination Therapy Part. The study is planned to run for a maximum of 3 years after the last patient's first dose. Enrolment has been completed in the ESC (N=9), and the DLBCL cohort of the Monotherapy Expansion Part (N=36). The DLBCL expansion cohort (N=36) provides supportive efficacy data for this submission.

As of the data cut-off date, 31 January 2022, the median follow-up was 8.4 months, 22 (61.1%) DLBCL patients discontinued epcoritamab treatment, of whom 20 patients (55.6%) discontinued treatment due to progressive disease and 2 patients (5.6%) discontinued treatment due to AE (both due to second primary malignancies not considered related to epcoritamab by the investigator). Fourteen (38.9%) patients in the DLBCL expansion cohort continued to receive epcoritamab treatment. All 13 patients (36.1%) who permanently discontinued the study had died.

In the DLBCL expansion cohort, all patients were of Asian race and Japanese ethnicity, 52.8% were female, and the median age was 68.5 years. The median duration of follow up was 8.4 months (range: 1.5, 12.0). Based on IRC assessment determined by Lugano criteria, the ORR (CR + PR) was 55.6% (95% CI: 38.1, 72.1) with 44.4% (95% CI: 27.9, 61.9) (n=16) and 11.1% (n=4) in patients achieving best response of CR and PR, respectively. The ORR was generally consistent across the prespecified subgroups.

The median DOR was not reached. The estimated percentages of patients remaining in response at 6 months and 9 months were 69.3% and 59.4%, respectively. For those achieving CR, 61.9% remained in CR at both 6 and 9 months. The median TTR and time to complete response (TTCR were 1.4 and 2.6 months, respectively.

Safety

A total of 374 patients with all B-NHL subtypes were assigned to receive 48 mg epcoritamab across the clinical trial program to date, including 208 patients with LBCL. Of those 157 participated in the EXP of study GCT3013-01, and of those, 139 had DLBCL.

Ten patients were not included in the safety analysis because they were allocated a treatment regimen and premedication regimen dose in the ESC Part of study GCT3013-01 that differed from the rest of study GC3013-01.

Two pooled safety datasets were also presented.

Pool 01 (N=167 patients) consists of all patients with LBCL assigned to receive the 48 mg full dose and received ≥1 dose of epcoritamab in the study GCT3013-01 (10 patients in the ESC and 157 patients in the EXP). Pool 01 comprised 148 patients with R/R DLBCL and 19 patients with non-DLBCL subtypes.

Pool 01+04 (N=374 patients) consists of all patients with all B-NHL subtypes (i.e., LBCL, iNHL, and MCL) assigned to receive the 48 mg full dose of epcoritamab and received ≥1 dose in the ESC and EXP parts of studies GCT3013-01 and GCT3013-04. This group includes 208 patients with LBCL, 128 patients with iNHL and 38 patients with MCL.

Treatment emergent adverse events

In patients with DLBCL in Study GCT3013-01, the median number of cycles initiated was 5.0 (range: 1, 20) and the median duration of treatment was 4.1 months (range: 0, 18).

Eighty three patients (59.7%) initiated Cycle 4 treatment (≥3 months of treatment), 42.4% initiated Cycle 7 (≥6 months treatment), 33.8% initiated Cycle 10 (≥9 months treatment), and 18.7% initiated Cycle 13 (≥12 months treatment).

In the DLBCL EXP cohort of Study GCT3013-01 (n=139), 99.3% of patients reported at least one treatment emergent adverse event (TEAE). The most commonly reported TEAEs (in ≥10% patients) were cytokine release syndrome (CRS; 48.9%), fatigue (23.7%), pyrexia, neutropenia (23.0% each), injection site reaction, diarrhoea, nausea (20.9% each), anaemia (18.7%), abdominal pain (15.1%), thrombocytopenia (14.4%), constipation, vomiting (12.9% each), headache (12.2%), oedema peripheral (11.5%).

In the same cohort, Grade 3 or 4 events were reported in 59.7% of patients, with the most common events (≥5%) neutropenia (22 patients [15.8%]), anaemia (16 patients [11.5%]), thrombocytopenia (8 patients [5.8%]) and neutrophil decreased (7 patients [5.0%]).

Treatment discontinuation due to TEAEs was reported for 7.9% of patients (11/139). Events occurring in ≥1 patient were COVID-19 infection and myelodysplastic syndrome (two patients each). Treatment/dose delay was reported for 33.1% of patients (46/139).

Safety in other study cohorts

Across the whole of the aNHL cohort of Study GCT3013-01 similar proportions of patients experienced adverse events.

Safety results in study-04 were generally consistent with those in the pivotal study. As of the data cutoff date, all 36 subjects in the DLBCL expansion cohort had experienced ≥1 TEAE. The most frequently reported were CRS (83.3%), injection site reaction (58.3%) and neutrophil count decreased (36.1%). Results from this study appear in the pooled data in Safety Pool 01+04.

In an analysis over time, using the Safety Pool 01 data set (Study GCT3013-01 ESC + EXP), the Sponsor demonstrated a higher adverse event rate inf the first 8 weeks of treatment for TEAEs, related events, Grade ≥3 events, SAEs, and adverse events of special interest (AESI) such as cytokine release syndrome, ICANs and clinical tumour lysis syndrome.

In safety Pool 01+04, Grade 3 or 4 TEAEs were reported for 66.0% of the DLBCL population and 63.9% of the all B-NHL population. The most frequently reported (≥5%) in the DLBCL

population were neutropenia (13.8%), anaemia, neutrophil count decreased (11.7% each), lymphocyte count decreased (8.0%), and thrombocytopenia (5.3%).

Treatment related adverse events (adverse drug reactions)

At least one epcoritamab-related TEAE (TRAE) was reported for 82.7% patients. The most frequently reported (≥10% patients) of these were CRS (48.9%), injection site reaction (20.9%), and neutropenia (18.7%), fatigue (13.7%), and pyrexia (10.8%). Most were reported as grades 1-2; but grade 3 or 4 events were reported in 27.3% of patients.

Deaths and other serious adverse events

Fatal (Grade 5) TEAEs occurred in nine patients (6.5%) DLBCL subjects. COVID-19, which occurred in two patients was the only fatal TEAE reported in more than 1 patient.

One fatal TEAE was considered related to epcoritamab by the investigator. This a 72-year-old female patient with a history of hyperlipidaemia, hypertension, diabetes, and paraesthesia was diagnosed with grade 3 pancreatitis on Day 10. The onset of immune effector cell-associated neurotoxicity syndrome (ICANS) was on Day 12, four days after the patient's second (and last) dose of epcoritamab (0.8 mg intermediate dose). Her course was complicated by Grade 1 CRS that resolved with tocilizumab, splenic infarction in the setting of thrombocytopenia and progressive disease.

In Safety Pool 01+04 fatal TEAEs were driven by the Study GCT3013-01 safety data. In the broader safety set, single fatal events of progressive multifocal leukoencephalopathy, necrotising fasciitis, pneumonia and sepsis were noted.

Overall, 57.6% of patients reported at least one SAE. The most frequent reported (≥2% were cytokine release syndrome (CRS) in 40 patients (28.8%), pleural effusion in 5 patients (3.6%), sepsis, ICANS, febrile neutropenia, and pyrexia in 4 patients each (2.9%), COVID 19 and pneumonia in 3 patients (2.2%).

The proportion of subjects with at least one epcoritamab-related SAE (TRSAE) was 35.3%, most frequently CRS (28.8%) and ICANS (2.9%).

In Safety Pool 01+04 SAEs were reported in 58.3% of the all-B-NHL population. The most commonly occurring (≥2%) were CRS (35.0%), pyrexia (2.7%), pneumonia, ICANS (2.4% each).

Adverse events of special interest

Cytokine release syndrome

In Study GCT3013-01 at least one CRS event was reported for 48.9% of patients. These 68 patients had a total of 98 CRS events. Most events were grade 1 (69.4% of events) and there were no Grade 4 or 5 events. The most common symptoms were fever (98.0%), hypotension (24.5%) and hypoxia (16.3%). CRS events were reported as a SAE in 28.8% of patients.

The median time to first CRS onset was 16.0 days (a median of 2.0 days (range: 1, 11)) from the most recent dose) and mostly occurred after the first full dose of epcoritamab. As of the data cut-off date, 96 (98.0%) CRS events had resolved, with the median time to resolution of 2.0 days (range: 1, 15).

The most common treatment reported for CRS was tocilizumab, that was received by 19 patients (27.9% of patients with CRS), with corticosteroids also used (13 patients, 19.1% of patients with CRS).

In Pool 01+04, 61.5% of all patients (all B-NHL) were reported to have had at least one CRS event. Of those 36.1% were Grade 1, 21.1% were Grade 2 and 4.0% were Grade 3 and 0.3% was Grade 4. No DLBCL patient had a Grade 4 event, but 4.3% had a Grade 3 event. Fever was reported in 61.2% of patients in this safety analysis, with hypotension in 20.3% and hypoxia in 11.5%. The median time to onset was also 16 days in this population but the onset was reported as early as one day and as late as 59 days in this broader safety set.

Immune effector cell-associated neurotoxicity syndrome

Immune Effector Cell-associated Neurotoxicity Syndrome (ICANS) is a pathological process in the CNS following immune therapy that results in the activation or engagement of endogenous or infused immune effector cells including T-cells. Symptoms can be progressive and may include aphasia, altered level of consciousness, impairment of cognitive skills, motor weakness, seizures, and cerebral oedema. Grading is based on the most severe event of any of: the 10-point immune effector cell-associated score (ICE score), level of consciousness, seizures, motor symptoms, and signs of raised intracranial pressure/cerebral oedema.

At least one ICANS event was reported for 6.5% of patients (9/139). Most of these were grade 1 events (4.3%; 6/139), two patients (1.4%) had grade 2 ICANS. There were no grade 3 or 4 events. One (0.7%) patient had fatal episode of ICANS, as described in the considerations of fatal TEAEs.

The median time to first onset of ICANS event was 17.0 days, correlating with the period shortly following the first full dose of epcoritamab on C1D15. As of the data cut-off date, ICANS events had resolved for 8 patients (88.9%) with the median time to resolution of 3.5 days.

ICANS resulted in a dose delay for threepatients and a dose discontinuation for 1 patient.

In Safety Pool 01+04, 6.1% of patients presented with at least one ICANS event. The median onset was 16.0 days (range 5, 141). All but one patient had resolution, and in a median time of two days (range 1, 9).

Clinical tumour lysis syndrome

In EXP Study GCT3013-01, 2 patients (1.3%) experienced events of CTLS, both of which were considered treatment-related within the setting of disease progression and were grade 3 in severity. Neither had resolved prior to the subjects' deaths (both due to disease progression). In Safety Pool 01+04 five patients experienced CTLS (including the patients from Study GCT3013-01).

Other adverse events

Cytopenias

The risk of cytopenia was predicted from the nonclinical studies.

Treatment-emergent post-baseline low absolute neutrophil count (ANC) was reported in 48.9% (64/131). Most were of worst grades 1 to 3 but grade 4 low ANC was reported in 14.5% (19/131). Similar proportions of events were reported for Pool 01+04.

Treatment-emergent post-baseline low platelets was reported in 48.5% (66/136). Most were of worst grades 1 to 3 but grade 4 low platelets were reported in 6.6% of DLBCL subjects (9/136). Similar proportions of events (±2%) were reported for Pool 01+04.

Treatment-emergent post-baseline low haemoglobin was 61.8% (84/136). All were of grades 1 to 3. Similar proportions of events (±2%) were reported for Pool 01+04.

Treatment emergent post-baseline low lymphocyte count reaching Grade 4 was reported in 51 patients in EXP of Study GCT3013-01 and was reported for 47.4% of all B-NHL patients in Safety Pool 01+04.

By grouped term, 39 patients (28.1%) had at least one adverse event of neutropenia, including 15 patients with grade 3 (10.8%) and 14 patients (10.1%) with grade 4 TEAEs. Febrile neutropenia was reported for 4 patients (2.9%), including 3 patients (2.2%) with grade 3 events and 1 patient (0.7%) with grade 4 event.

Analyses of cytopenia TEAEs by analysis periods showed that thrombocytopenia and anaemia events mainly occurred during the first 8 weeks, whereas neutropenia events were more evenly distributed across the first 36 weeks.

Injection site reactions

Around 29.5% of patients (41/139) reported at least 1 TEAE of Injection Site Reaction (ISR). The events resolved in 95.1% of cases. All ISR events were either grade 1 (27.3%; 38/139) or grade 2 (2.2%; 3/139) in severity.

In the Safety Pool 01+04 All B-NHL 40.1% of patients experienced ≥1 injection site reaction. The maximum grade was Grade 1 (34.0%) or Grade 2 (6.1%).

The highest proportion of events occurred in the first eight weeks of treatment (36.9%) and decreased to 13.0% during the Week 36+ period.

Infections

Infections were reported as TEAEs for 61 patients (43.9%), most commonly (≥5.0%) were pneumonia (8 patients [5.8%]), urinary tract infection (7 patients [5.0%]), and COVID-19 (7 patients [5.0%]).

Infections were reported as SAEs for 22 patients (15.8%), most commonly sepsis (4 patients [2.9%]), and COVID-19 and pneumonia (3 patients [2.2%]) each. TRSAEs of sepsis, upper respiratory tract infection, and oral herpes were each reported for 1 patient (0.7%).

In Safety Pool 01+04 All B-NHL population, 46.5% reported at least one TEAE, and were considered related to epcoritamab in 11.5%. SAEs were reported in 18.7%, and fatal events in 2.4%. An analysis by time period showed a reasonably consistent risk of infection throughout treatment. The types of events were similar to those reported in the EXP Study GCT3013-01 DLBCL cohort.

Other considerations

Subgroup analyses of safety by intrinsic factors (age, sex, race, baseline weight, baseline renal function, baseline hepatic function, and Ann Arbor staging) in the pooled safety datasets did not trigger any major safety concerns. There is no clinical safety data in pregnant/lactating women.

No clinical studies investigated the potential for DDIs between epcoritamab and other drugs. Given the primary elimination pathway for epcoritamab is presumed to be protein catabolism, direct DDIs between epcoritamab and other small molecule drugs are considered unlikely, however cytokine release may modulate CYP450 enzyme activity.

Subgroup analyses of safety by extrinsic factors (geographic region, prior lines of anti-lymphoma therapy, and prior treatment with CAR-T cell therapy) in the pooled safety datasets did not trigger any major safety concerns.

Clinical study plan

Data from three clinical trials were proposed by the Sponsor as the clinical study plan as part of the provisional determination application, and as included in the Australian Specific Annex of the EU-RMP:

1. Study GCT3013-05: a randomised, open-label, Phase 3 trial of epcoritamab vs investigator's choice chemotherapy in R/R DLBCL patients who have failed or are ineligible for high dose therapy – autologous stem cell transplant. The investigator's choice will be either rituximab + gemcitabine + oxaliplatin (R-GemOx) or bendamustine + rituximab. The primary endpoint is overall survival. The trial is ongoing and at the time of lodgement of the provisional determination application, 410 of the planned 480 patients had enrolled (85% accrual), and a submission in Q4 2024 is proposed.
2. Study GCT3013-01
3. Study GCT3013-04

A condition of registration to implement the Clinical Study Plan will be imposed. A question has been included for the Sponsor regarding the Clinical Study Plan. This section will be updated and the wording of the conditions of registration relating to the Clinical Study Plan provided once the Sponsor's response to the question has been received.

Risk management plan evaluation summary

AbbVie Pty Ltd submitted Core Risk Management Plan (RMP) version 1.0 (dated September 2022; data lock point 31 January 2022) and Australia-specific annex (ASA) version 1.0 (dated February 2023). The Sponsor subsequently provided EU RMP version 1.4 (dated July 2023; data lock point 31 January 2022) and ASA version 2.0 (dated October 2023).

Safety concerns and their associated risk monitoring and mitigation strategies are summarised in Table 4.

Table 4. Summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Cytokine release syndrome (CRS)	✓*	✓†	✓	✓‡
	Immune Effector Cell-associated Neurotoxicity Syndrome (ICANS)	✓*	✓†	✓	✓‡
Important potential risks	Serious infections	✓	✓†	✓	
Missing information	Long-term safety	✓	✓†		

*Targeted follow up questionnaire
†Clinical trial
‡Patient alert card

The safety concerns outlined in the EU RMP are consistent with those presented in the ASA. The special warnings and precautions mentioned in the PI are addressed in the list of safety concerns.

The Sponsor has proposed routine pharmacovigilance for all safety concerns and specific follow-up questionnaires for CRS and ICANS. Additional pharmacovigilance activities via ongoing clinical trial monitoring is proposed for all safety concerns. The pharmacovigilance plan in the EU RMP align with the ASA and is acceptable from an RMP perspective.

Routine risk minimisation has been proposed for all safety concerns except missing information 'long-term safety'. Additional risk minimisation material is proposed for safety concerns 'CRS' and 'ICANS' in the form of a patient alert card to be distributed by the prescriber. A mock-up of the card has been provided for review at Round 2. A further amendment to patient card to cross reference the CMI for further information should be provided to the TGA for review and acceptance prior to launch. EPKINLY is to be included in the Black Triangle Scheme.

Risk-benefit analysis

The Sponsor has proposed provisional approval for epcoritamab for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy. The Evaluators found efficacy and safety and the RMP support approval.

Both the main study (GCT3013-01) and the supportive study (GCT3013-04) enrolled patients who had relapsed, progressive and/or refractory B-cell lymphoma, with R/R DLBCL being a subgroup within the studies.

Epcoritamab is proposed for subcutaneous dosing. The pharmacokinetics of epcoritamab was best described by a two-compartment model with first-order subcutaneous absorption, target mediated drug disposition. It has saturable target mediated clearance and a concentration dependent half-life. Population pharmacokinetic modelling estimated the half-life to be 22 to 25 days. Around 2.5% of patients developed ADAs, but there were insufficient data to draw any robust conclusions about the impact of this observation on efficacy and/or safety.

Efficacy results were supportive of a positive effect of epcoritamab in patients with R/R DLBCL who have received two or more prior lines of systemic therapy. In patients with R/R DLBCL treated with epcoritamab in study GCT3013-01 at the 31 January 2022 DCO:

- 47/139 (33.8%) patients were continuing epcoritamab treatment.
- median number of cycles initiated was 5.0 (range: 1, 20)
- median duration of treatment was 4.1 months (range: 0, 18)
- median duration of follow-up was 11.0 months (range: 0.3, 17.9).
- ORR (95%CI) was 61.9% (53.3, 70.0) and CR (95%CI) was 38.8% (30.7, 47.5).
- median DOR for patients who had achieved PR or CR was 12.0 months (95% CI: 6.6, NR)
- median DOR for patients who had achieved CR was not reached (95% CI: 12.0, NR),
- median DOCR was 12.0 months (95% CI: 9.7, NR).
- estimated % of patients remaining in response at 9 months was 61.6% (all responders) and 87.8% (complete responders).

- median TTR was 1.4 months (range: 1.0, 8.4) for all responders and median TTCR was 2.7 months (range: 1.2, 11.1).

Efficacy is at least comparable with other similar treatments, but the long-term durability of response is yet to be tested in this population. The Sponsor notes in the submission that CAR T-cell therapy, while having good initial responses has been reported in some instances to have a relapse rate in excess of 40%. While the preliminary clinical data support a durable effect, longer follow up and a larger patient cohort, both of which are planned by the Sponsor, will be needed before any meaningful conclusions can be reached.

The patient population was heavily pre-treated. Notwithstanding the limitations of subgroup analysis of what is already a subgroup of a larger patient cohort, there is early evidence to support efficacy in patients who have relapsed after CAR T-cell therapy or have previously received a stem cell transplant. This suggests a place in therapy not only for the transplant or CAR-T-cell ineligible patient population.

The safety of epcoritamab was primarily supported by safety data from 139 patients with R/R DLBCL from Study GCT3013-01. Additional safety data were derived from an analysis of data from two safety pools. In all 374 patients with a B-cell NHL contributed safety data.

The key safety concerns are the risks of CRS, ICANS, cytopenias, infections, injection site reactions and clinical tumour lysis syndrome.

CRS is potentially life threatening. The minimise the risk of severe CRS in study GCT3013-01 the Sponsor excluded of patients with a high number of circulating lymphocytes at screening (>5 × 109/L); required premedication with corticosteroids, antihistamines, and antipyretics; used a low first dose (priming dose) and second dose (intermediate dose) than the subsequent doses of epcoritamab; and required hospitalisation during the expected maximum circulation levels of epcoritamab for the first administrations. In addition, patients with markedly decreased creatinine clearance (<45 mL/min) or markedly impaired cardiac function (onset of unstable angina pectoris within 6 months of signing ICF, acute myocardial infarction within 6 months of signing ICF or congestive heart failure [grade III or IV as classified by the New York Heart Association] and/or known decrease ejection fraction of <45%) were excluded from the study.

The CRS treatment protocol in Study GCT3013-01 included hospitalisation for a new fever, with management of potential neutropenia, intravenous fluids ± vasopressors for hypotension, radiographic investigation, and an escalating regimen of respiratory management for hypoxia, consideration of tocilizumab for Grade 2 disease, with recommendation for its use in more severe Grades. Patients with Grade 4 CRS could not continue treatment and high-dose steroid prophylaxis for each subsequent epcoritamab dose was used for any patient with a Grade 2 or 3 events until CRS was no longer a feature post dosing. With these strategies in place, CRS was reported in 48.9% of patients in the EXP of Study GCT3013-01, but most events were Grade 1.

While hospitalisation was required for the first dose of epcoritamab, the Sponsor proposes only to require patients to be in 'close proximity' of the health facility rather than requiring hospitalisation, although that could be an option based on the clinical judgement of the treating clinician.

ICANS is also a potentially life-threatening event, and it did contribute to one fatal AE in the clinical trials. The Sponsor proposes to include information about ICANS on the patient card and has recommendations for treatment based on clinical features proposed for the EPKINLY PI.

The prescribers of this medicine will be haematologists, who will be familiar with the adverse event profile of similar medicines to epcoritamab. The patient card, patient education and the PI information will be of importance for other health professionals caring for the patient. A low index of suspicion is needed for early detection of CRS and ICANS, and prompt management,

given the non-specific nature of early symptoms, and the potential for concurrent adverse events (e.g. CRS and ICANS in the same patient).

Cytopenias, infections, and TLS in bulky disease are not unexpected given the mechanism of action and are generally considered manageable by haematologists. Injection site reactions were also mostly < Grade 2 and therefore potentially manageable.

While 374 patients in total have been exposed, the exposure in the population requested for the indication is more limited. Long term safety, including the long-term risk of secondary malignancy is not yet available. There are limitations in both numbers of patients and duration of follow up that are expected to be addressed with further data from the current studies and the ongoing Phase 3 study GCT3013-05.

Epcoritamab is an off-the-shelf product, given subcutaneously that can be given without the delays necessary for CAR-T therapy and that it is given subcutaneously, which could be seen to be advantageous.

The Sponsor proposes to include a disclaimer about the use of epcoritamab in primary CNS lymphoma. The Indication statement is usually limited to the condition for which use is intended rather than examples of a much longer list of potential conditions in which the medicine has not been studied. In considering whether the proposal is acceptable, the approval of the similar product glofitamab, the advice of the TGA's Advisory Committee on Medicines (ACM) on this point and the provisional nature of the requested registration of epcoritamab, was considered. For consistency in approach, the indication is accepted in the setting of provisional registration. The wording of the indication statement may require reconsideration if the Sponsor proposes to convert the provisional registration to full registration at a later date.

The proposed dosing regimen is the same as that investigated in the main study. The dosing instructions in the PI could be improved by the transposition or the Cycle of Treatment column and the Dosing schedule column.

Administration instructions are needed to avoid medication error in the dilution of epcoritamab for the priming dose and the intermediate dose. Epcoritamab is not intended for patient administration, and while the TGA no longer requires the PI to be included in the packaging of an injectable prescription medicine administered by a health professional, administration instructions will be needed to be included as a package insert in the EPKINLY packaging as a risk mitigation strategy.

Conclusions

Based on the preliminary clinical data an ORR of 61.9% in the main population tested is considered clinically meaningful in this later line setting in R/R DLBCL disease, as is the median DOR of 12 months. The safety profile to date is consistent with other bispecific antibodies that have been studied in haematological malignancies. The CRS and ICANS events, in particular, require clinical vigilance and early active management however the prescriber cohort will be familiar with the risks and their management. Overall, based on these preliminary clinical data the benefits appear of sufficient magnitude to outweigh the risks as they have been characterised in the submission.

Assessment outcome

Based on a review of quality, safety, and efficacy, the TGA decided to register EPKINLY (epcoritamab) for the following 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. EPKINLY is not indicated for the treatment of patients with primary central nervous system lymphoma.

This medicine has provisional approval in Australia for the treatment of adult patients with relapsed or refractory DLBCL after two or more lines of systemic therapy. The decision to approve this indication has been made on the basis of overall response and duration of response from an uncontrolled, open label phase I/II study. Continued approval of this indication depends on verification and description of benefit in confirmatory trials.

The decision to approve this indication has been made on the basis of CR and the ORR from an uncontrolled, open label phase I/II study. Continued approval of this indication depends on verification and description of benefit in confirmatory trials

Specific conditions of registration

EPKINLY (epcoritamab) is to be included in the Black Triangle Scheme. The PI and CMI for EPKINLY must include the black triangle symbol and mandatory accompanying text for five years, or the product's entire period of provisional registration, whichever is longer.

The EPKINLY EU-Risk Management Plan (RMP) (version 1.4, dated July 2023, data lock point 31 January 2022), with Australian Specific Annex (version 3.0, dated January 2024), included with submission PM-2023-00662-1-6, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

Unless agreed separately between the supplier who is the recipient of the approval and the TGA, the first report must be submitted to TGA no later than 15 calendar months after the date of this approval letter. The subsequent reports must be submitted no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of this approval letter, or the entire period of provisional registration, whichever is longer.

The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within ninety calendar days of the data lock point for that report.

All batches of EPKINLY supplied in Australia must comply with the product details and specifications approved during evaluation and detailed in the Certified Product Details (CPD).

When requested by the TGA, the Sponsor should be prepared to provide product samples, specified reference materials and documentary evidence to enable the TGA to conduct laboratory testing on the Product. Outcomes of laboratory testing are published biannually in the TGA Database of Laboratory Testing Results http://www.tga.gov.au/ws-labs-index and periodically in testing reports on the TGA website.

The Certified Product Details (CPD), as described in Guidance 7: Certified Product Details of the Australian Regulatory Guidelines for Prescription Medicines (ARGPM) http://www.tga.gov.au/industry/pm-argpm-guidance-7.htm, in PDF format, for the above products should be provided upon registration of these therapeutic goods. In addition, an updated CPD should be provided when changes to finished product specifications and test methods are approved in a Category 3 application or notified through a self-assessable change.

The Sponsor must conduct studies as described in the clinical study plan in version 3.0 (date January 2024) of the Australia-Specific Annex. Study report GCT3013-05 should be submitted to the TGA for evaluation.

Product Information and Consumer Medicines Information

For the most recent Product Information (PI) and Consumer Medicines Information (CMI), please refer to the TGA PI/CMI search facility.

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