EU Risk Management Plan for Epcoritamab

AbbVie Inc. (AbbVie)/Genmab

RMP version to be assessed as part of this application:

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Rationale for submitting an updated RMP: For Protocol GCT3013-05, the primary analysis CSR planned date has been revised to Quarter 2 of 2026.

Summary of significant changes in the RMP: A summary of significant changes is included in RMP Annex 8.

Administrative Information on the RMP

Part Module/Annex	Date last updated for submission (sign-off date)	Version number of RMP when last submitted
Part 1: Product(s) Overview	March 2024	2.1
Part II: Safety Specification	NA	1.0
SI – Epidemiology of the Indication(s) and Target Population(s)	November 2023	2.0
SII – Non-Clinical Part of the Safety Specification	NA	1.0
SIII – Clinical Trial Exposure	March 2024	2.1
SIV – Populations Not Studied in Clinical Trials	March 2024	2.1
SV – Post-Authorization Experience	November 2023	2.0
SVI – Additional EU Requirements for the Safety Specification	NA	1.0
SVII – Identified and Potential Risks	March 2024	2.1
SVIII – Summary of the Safety Concerns	March 2024	2.1
Part III: Pharmacovigilance Plan (Including Post-Authorization Safety Studies)	June 2024	2.2
Part IV: Plan for Post-Authorization Efficacy Studies	NA	1.0
Part V: Risk Minimization Measures (Including Evaluation of the Effectiveness of Risk Minimization Activities)	July 2023	1.4
Part VI: Summary of the Risk Management Plan	November 2023	2.0
Part VII: Annexes	NA	1.0
Annex 2 – Tabulated Summary of Planned, Ongoing, and Completed Pharmacovigilance Study Program	June 2024	2.2
Annex 3 – Protocols for Proposed, Ongoing, and Completed Studies in the Pharmacovigilance Plan	November 2023	2.0
Annex 4 – Specific Adverse Drug Reaction Follow-Up Forms	September 2022	1.0
Annex 5 – Protocols for Proposed and Ongoing Studies in RMP Part IV	NA	1.0
Annex 6 – Details of Proposed Additional Risk Minimization Activities (If Applicable)	March 2023	1.1
Annex 7 – Other Supporting Data (Including Referenced Material)	November 2023	2.0

Annex 8 – Summary of Changes to the Risk Management Plan Over Time	June 2024	2.2
Annex 9 – Local Currently-Approved Country Labeling	NA	
Annex 10 – Local Risk Management/Mitigation Plan	NA	

NA = Not Applicable

Other RMP versions under evaluation: Not Applicable

QPPV Name: Sina Schader

QPPV oversight declaration: The content of the RMP has been reviewed and approved by the marketing authorization holder QPPV through an electronic document system per company standard operating procedure.

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List of Abbreviations

AE	adverse event
Allo-SCT	allogenic stem cell transplantation
ALT	alanine transaminase
ASCT	autologous hematopoietic stem cell transplantation
AST	aspartate transaminase
ATC	anatomical therapeutic chemical
BCL	B-cell lymphoma
B-NHL	B-cell non-hodgkin lymphoma
BR	bendamustine + rituximab
BRM	benefit-risk management
CAR T-cell	chimeric antigen receptor t-cell
CD	cluster of differentiation
CHO	chinese hamster ovary
CHOP	cyclophosphamide, doxorubicin, vincristine, and prednisone
CI	confidence interval
CNS	central nervous system
CRS	cytokine release syndrome
CSR	clinical study report
CTLS	clinical tumor lysis syndrome
CxDx	cycle x day x
DA-EPOCH-R	etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab
DH/TH	double hit or triple hit
DLBCL	diffuse large b-cell lymphoma
DLP	data lock point
DLT	dose-limiting toxicity
ECIS	European cancer information system
EEA	European economic area
EMA	European medicines agency
EPAR	European public assessment report
ESC	escalation
EXP	expansion
EU	European union
FL	follicular lymphoma
FLIPI	follicular lymphoma international prognostic index

GemOx	gemcitabine and oxaliplatin
GLP	good laboratory practice
GVP	guideline on good pharmacovigilance practices
HCP	health care professional
HDT	high dose therapy
HGBCL	high grade b-cell lymphoma
HIV	human immunodeficiency virus
HMRN	haematological malignancy research network
IC	investigator's choice
ICANS	immune effector cell-associated neurotoxicity syndrome
IDMC	independent data monitoring committee
IgG	immunoglobulin g
INN	international nonproprietary name
IPI	international prognostic index
IV	intravenous
LBCL	large b-cell lymphoma
LYRIC	lymphoma response to immunomodulatory therapy criteria
MAH	marketing authorisation holder
MCL	mantle cell lymphoma
MedDRA	medical dictionary for regulatory activities
MTD	maximum tolerated dose
MZL	marginal zone lymphoma
NHL	non-hodgkin lymphoma
NOS	not otherwise specified
OS	overall survival
PD	progressive disease
PMBCL	primary mediastinal b-cell lymphoma
PRAC	pharmacovigilance risk assessment committee
PRO	patient reported outcome
PT	preferred term
PV	pharmacovigilance
PY	patient years
R^2	rituximab and lenalidomide
R-CHOP	rituximab plus cyclophosphamide, hydroxydaunorubicin, oncovin, and prednisone

R-CODOX-M/IVAC	rituximab, cyclophosphamide, doxorubicin, vincristine, methotrexate/ifosfamide, etoposide, high dose cytarabine
R-GemOx	rituximab, gemcitabine, and oxaliplatin
R-hyper-CVAD	rituximab, cyclophosphamide, vincristine, adriamycin, and dexamethasone
R-IPI	revised international prognostic index
RMP	risk management plan
RP2D	recommended phase 2 dose
R/R	relapsed or refractory
RS	relative survival
QPPV	qualified person responsible for pharmacovigilance
Q2W	every 2 weeks
Q4W	every 4 weeks
QW	once weekly
SC	subcutaneous(ly)
SCS	summary of clinical safety
SCT	stem cell transplant
SDRC	safety and dosing review committee
SEER	surveillance, epidemiology, and end results
SLL	small lymphocytic lymphoma
SmPC	summary of product characteristics
SOC	standard of care
SUD	step-up dosing
TBIL	total bilirubin
TEAE	treatment-emergent adverse event
TLS	tumor lysis syndrome
ULN	upper limit of normal
US	United States
vs	versus

Part I: Product(s) Overview

Table 1. Product Overview

Active substance(s) (INN or common name)	Epcoritamab
Pharmacotherapeutic group(s) (ATC Code)	Antineoplastic (ATC Pending)
Marketing Authorization	AbbVie Deutschland GmbH & Co. KG
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Tepkinly
Marketing authorization procedure	Centralized
Brief description of the product	Chemical class: Humanized IgG1-bispecific antibody
	Summary of mechanism of action: Binds to a specific extracellular epitope of CD20 on B cells and to CD3 on T cells.
	Important information about its composition: • Manufactured from 2 biological intermediates, which are produced in Chinese hamster ovary (CHO) cells using recombinant DNA technology and has an approximate molecular weight of 149 kDa. • Has a regular IgG1 structure and biochemical characteristics typical of human IgG1. • 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.
Hyperlink to the Product Information	The SmPC is used for the relapsed or refractory (R/R) diffuse large B-cell lymphoma (DLBCL) and R/R follicular lymphoma (FL) indications.
Indication(s) in the EEA	**Current DLBCL**: Epcoritamab is indicated for the treatment of adult patients with R/R DLBCL after 2 or more lines of systemic therapy.
	Proposed for FL (Grades 1-3A): Epcoritamab is indicated for the treatment of adult patients with R/R FL after 2 or more lines of systemic therapy. The indication(s) may differ outside of the EEA.

Dosage in the EEA	**Current for DLBCL**: Epcoritamab is administered subcutaneously (SC) in treatment cycles of 28 days. The 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 at C1D15, C1D22, and thereafter, administered according to the following schedule: • Cycles 2 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 • Cycles 10 and beyond until unacceptable toxicity or progressive disease (PD): once every 4 weeks (Q4W) on Day 1
	Proposed for FL (1-3A): Epcoritamab is administered SC in treatment cycles of 28 days. The 3-step step-up dosing (SUD) regimen includes an initial priming dose of 0.16 mg (C1D1), a first intermediate dose of 0.8 mg (C1D8), a second intermediate dose of 3 mg (C1D15), and a full dose of 48 mg at C1D22, and thereafter, administered according to the following schedule: • Cycles 2 to 3: once QW on Days 1, 8, 15, and 22 • Cycles 4 to 9: once Q2W on Days 1 and 15 • Cycles 10 and beyond until acceptable toxicity or PD: once Q4W on Day 1
Pharmaceutical form(s) and strengths	**Current:** • Solution for injection (4 mg/0.8 mL); • Solution for injection (48 mg/0.8 mL)
	Proposed: Not Applicable
Is/will the product be subject to additional monitoring in the EU?	Yes

Part II: Safety Specification

Module SI Epidemiology of the Indication(s) and Target Population(s)

Indication: Diffuse large B-cell lymphoma (DLBCL) (EU)

Treatment of adult patients with R/R DLBCL after 2 or more lines of systemic therapy

Incidence:

DLBCL is an aggressive type of non-Hodgkin lymphoma (NHL) that develops from the B-cells in the lymphatic system. It is the most common type of NHL, accounting for 30% to 40% of NHL (Sethi 2019).

LBCL is a heterogeneous collection of clinicopathological entities, which includes DLBCL (not otherwise specified [NOS]) (accounting for >80% of cases of LBCL), follicular lymphoma [FL] grade 3b, primary mediastinal B-cell lymphoma [PMBCL], high grade B-cell lymphoma (HGBCL) with MYC and B-cell lymphoma (BCL) 2 and/or BCL6 rearrangements and HGBCL, NOS (Sehn 2021).

EU

The most up-to-date European Cancer Information System (ECIS) provides incidence of NHL but not subtypes in the EU for 2020 (ECIS - European Cancer Information System).

The incidence of DLBCL in the EU-27 was estimated by multiplying the incidence of NHL in the EU-27 for 2020 (18.3/per 100,000, age standardized rate [European new]) by the proportion of DLBCL (NOS) in NHL from Haematological Malignancy Research Network (HMRN; 40.6%) (ECIS - European Cancer Information System , Haematological Malignancy Research Network (HMRN)). The estimated incidence of DLBCL was 7.4 (9.0 in males and 6.2 in females) per 100,000 for 2020 in the EU-27 and ranged from 3.5 (Bulgaria) to 11.4 (Slovenia) per 100,000. (Smith 2015b).

The estimated incidence of DLBCL in the EU-27 for 2020 by age group (40 to 54, 55 to 69, and 70 to 84 years) was 5.0, 13.1, 24.0 per 100,000, respectively.

US

Based on the Surveillance, Epidemiology, and End Results (SEER) Program and Cancer Statistics Review, the age-adjusted incidence of DLBCL in the US from 2015 to 2019 was 5.6 per 100,000 per year (6.7 in males and 4.6 in females) (National Cancer Institute 2022a). The percent of new cases by age group (45 to 54, 55 to 64, 65 to 74, 75 to 84, > 84 years) was 11.5%, 21.2%, 26.2%, 20.0%, and 8.4%, respectively (National Cancer Institute 2022a).

FL grade 3b is fast growing and accounts for 5% to 10% of FL (Barraclough 2021). The age-adjusted incidence of FL in the US from 2015 to 2019 was 2.6 per 100,000 per year (2.8 in males and 2.4 in females). The percent of new cases by age group (45 to 54, 55 to 64, 65 to 74, 75 to 84, > 84 years) was 16.2%, 27.5%, 27.5%, 15.3%, 4.8%, respectively (National Cancer Institute 2022b).

PMBCL accounts for about 2% to 4% of NHL (National Cancer Institute 2022c). The annual incidence of PMBCL was 0.04 per 100,000 (Yu 2021).

The proportion of HGBCL with MYC and BCL2 and/or BCL6 rearrangements in DLBCL was estimated to be 1% to 12% (Scott 2018). HGBL, NOS accounts for 3% of the adult invasive BCLs (Li 2020).

LBCL incidence is estimated to be 5.9 per 100,000 per year in the US (DLBCL, 5.6; FL grade 3b, 0.26; PMBCL, 0.04).

Prevalence:

EU

According to the Orphanet Report Series, the estimated DLBCL prevalence in Europe (age-adjusted to the European population) was 4.3 per 10,000 (Orphanet 2020).

The prevalence of DLBCL in the EU-27, plus Iceland, Liechtenstein, and Norway in 2020 was estimated to be 4 per 10,000 individuals (European Medicines Agency 2022c).

US

The prevalence of DLBCL in the US was estimated by multiplying the annual DLBCL incidence in the US derived from the SEER Program (5.6 per 100,000; 18,873.41 new cases per year) by the estimated disease duration (overall survival [OS], 5.0 years) (Costa 2014, National Cancer Institute 2022a). The resulting prevalence estimate was 28.0 per 100,000 (93,216 cases) in the US with DLBCL.

Demographics of the target population:

DLBCL is more common in males than females and occurs mostly in older people (see incidence data by gender and age group above). The average age at the time of diagnosis is mid-60s (National Cancer Institute 2022a). Incidence varies by ethnicity, with Caucasians having higher risks compared to Blacks, Asians, or other races (Morton 2006, Shirley 2013, Smith 2011).

A more recent study reported DLBCL incidence and relative survival (RS) in the Netherlands by age, sex, and stage of disease (Durmaz 2022). By stage, the age-adjusted incidence during 2011 to 2018 (per 100,000 per year) was 5.4 overall, 1.0 for stage 1, and 4.2 for stages 2 to 4. The incidence for all stages (per 100,000) was 4.4 in those 20 to 64 years of age, 22.2 in those 65 to 74 years of age, and 34.9 in those ≥ 75 years of age. Specifically for stages 2 to 4, the incidence (per 100,000 per year) was 3.5 in those 20 to 64 years of age, 17.9 in those 65 to 74 years of age, and 26.0 in those ≥ 75 years of age.

Similar to DLBCL, FL grade 3b occurs mostly in older people and more commonly in males (Barraclough 2021). Unlike other NHL subtypes, PMBCL occurs mostly in adolescents and young adults (median age, 35 years) with female predominance (National Cancer Institute 2022c).

Risk Factors:

The etiology of DLBCL remains poorly understood. Risk increases with age and is higher in males and Caucasians (Haematological Malignancy Research Network (HMRN) , Howlader 2020, National Cancer Institute 2022a). Other potential risk factors include a family history of lymphoma, genetic susceptibility loci (tumor necrosis factor/lymphotoxin-alpha; 6p25.3; 6p21.33; 2p23.3; 8q24-21), viruses (Epstein-Barr Virus, human immunodeficiency virus [HIV], herpes virus type 8, hepatitis B, hepatitis C), solid-organ transplantation, B-cell-activating autoimmune disorders (systemic lupus erythematosus, Sjögren's syndrome, celiac disease), immunodeficiency, increased body-mass index (in young adults), agricultural pesticides, and ionizing radiation (Sehn 2021).

No specific risk factors have been identified for FL grade 3b and PMBCL (Martelli 2017).

The main existing treatment options:

DLBCL is a rapidly advancing cancer that requires immediate treatment. The standard first-line therapy for DLBCL is the combination of cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP), or a similar "CHOP-like" regimen, with rituximab (R-CHOP) (National Comprehensive Cancer Network 2021). Approximately a third of patients are refractory to or relapse after R-CHOP within 5 years of diagnosis (Cunningham 2013).

For R/R DLBCL patients after frontline chemoimmunotherapy, the sole option for long-term survival is salvage therapy, followed by high dose therapy (HDT) and autologous hematopoietic stem cell transplantation (ASCT). However, only half of the patients with R/R DLBCL are eligible to receive HDT-ASCT, and among those who are transplant-eligible, some are insensitive to salvage therapy, precluding ASCT (Gisselbrecht 2012, Hamadani 2014). For the patients who relapse or are ineligible for second line HDT-ASCT, patients will normally be offered non-intensive salvage therapy (e.g., gemcitabine and oxaliplatin [GemOx] with or without rituximab, bendamustine with or without rituximab, pixuvri) or other palliative intervention (Corazzelli 2009, National Comprehensive Cancer Network 2021, Vacirca 2014, Zelenetz 2021).

Recently, multiple drugs have been approved for R/R DLBCL. Chimeric antigen receptor t-cell (CAR T-cell) therapies (tisagenlecleucel, axicabtagene ciloleucel, and lisocabtagene maraleucel) are approved for patients with R/R DLBCL after at least 2 lines of therapy in the US and EU. Polatuzumab vedotin in combination with bendamustine + rituximab (BR) is approved for third-line patients with R/R DLBCL in the US and second line in EU (if not eligible for ASCT); however, it is limited in many regions and is only an option for patients whose disease is sensitive to chemotherapy. Tafasitamab (in combination with lenalidomide) is approved in the EU for the treatment of adult patients with R/R DLBCL.

FL grade 3b is often treated as DLBCL (Dreyling 2021). Historically R-CHOP has been the usual first line treatment for PMBCL followed by involved site radiotherapy, however recent studies

have shown excellent responses with etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab (DA-EPOCH-R) with omission of consolidative mediastinal RT. For R/R PMBCL, salvage chemoimmunotherapy followed by ASCT provides a best chance of long-term disease control. Despite excellent responses to first-line therapy, outcomes of R/R PMBCL remain poor. Breyanzi and Yescarta have been recently approved for the treatment of adult patients with R/R PMBCL after at least 2 lines of therapy in the US and EU. Keytruda is approved for third- or later lines PMBCL in the US and not approved in EU. Patients with HGBCL are typically treated with standard R-CHOP or more aggressive regimens such as DA-EPOCH-R, rituximab, cyclophosphamide, vincristine, adriamycin, and dexamethasone (R-hyper-CVAD) or rituximab, cyclophosphamide, doxorubicin, vincristine, methotrexate/ifosfamide, etoposide, high dose cytarabine (R-CODOX-M/IVAC) (Decker 2020, Ok 2020).

Natural history of the indicated disease/condition in the untreated population, including mortality and morbidity:

DLBCL is ideally diagnosed from an excisional biopsy of a suspicious lymph node, which shows sheets of large cells that disrupt the underlying structural integrity of the follicle center of the lymph node and stain positive for pan-B-cell-antigens, such as CD20 and CD79a. DLBCL is a heterogeneous disease and can be classified in multiple ways: clinically, by morphology, or by immunohistochemical and molecular subgroups (Gatter 2010, Hans 2004, Scott 2014, Wright 2003).

DLBCL can present as de novo disease or occur as a transformation from low-grade BCLs such as FL or chronic lymphocytic leukemia/small lymphocytic lymphoma (SLL). DLBCL is divided into 4 stages based upon involvement of lymph nodes and extranodal sites. Approximately 40% of DLBCL is stage 1/2 (localized) and 60% is stage 3/4 (advanced) at the time of diagnosis (Smith 2015b). At least one-third of DLBCL becomes R/R, and 70% of R/R DLBCL (at least 25% of DLBCL overall) are transplant-ineligible or chemo-refractory (Sarkozy 2018).

The disease typically begins as a rapidly growing mass in a lymph node or other organ. If left untreated, patients with DLBCL have a median survival of less than 1 year (Rovira 2015). Initial treatment with R-CHOP results in cure in approximately 50% to 70% of patients overall (Liu 2019, Sarkozy 2018). Patients who achieve event-free status at 24 months from diagnosis have a subsequent OS that is comparable to the general population (Maurer 2014).

For patients whose disease is refractory to initial treatment or relapses after achieving remission, the outcomes are poor (Liu 2019). Approximately 10% to 15% of all DLBCL patients treated with R-CHOP will fail within 1 year of diagnosis, and these patients with early R/R disease have a very poor prognosis (Sarkozy 2018). An additional 20% to 30% of all DLBCL patients will have a later relapse of disease.

For patients with R/R DLBCL, the current preferred treatment is salvage chemotherapy followed by HDT-ASCT. Due to advanced age or existing comorbid conditions a significant proportion of patients are ineligible for ASCT. Among those who are eligible for ASCT, only approximately 40% receive ASCT, mainly due to non-response to salvage therapy (Sarkozy 2018).

PMBCL was previously classified as a DLBCL subtype. Due to its unique clinical, histological, and molecular characteristics, PMBCL has been listed as a separate type in lymphoma classification by the World Health Organization since 2016 (Swerdlow 2016).

PMBCL is an aggressive LBCL originating in the mediastinum, that mainly expresses B cell surface molecules, such as CD19, CD20, CD22, andCD79a. Clinically, they are characterized by rapidly increasing anterior mediastinal masses, which can cause compression of the surrounding tissues. The involvement of distant lymph nodes and bone marrow is rare. Symptoms develop rapidly, usually within a few weeks of disease onset. Eighty percent of cases are diagnosed as stage 1 to 2 (Yu 2021).

FL grade 3b is a special category in which the neoplasm is composed exclusively of centroblasts, without admixed centrocytes. Studies have reported that FL grade 3b exhibits a lower frequency of CD10 antigen expression and t(14;18) chromosomal translocation, both markers seen in a high proportion of FL grades 1 to 3a. By contrast, cytoplasmic immunoglobulin expression and the presence of chromosome band 3q27 rearrangement, features associated more commonly with DLBCL, were seen more commonly in FL grade 3b (Shustik 2011).

HGBCL with MYC and BCL2 and/or BCL6 rearrangements (i.e., double hit or triple hit [DH/TH] lymphoma) shows variable morphologies including DLBCL, BCL-unclassified or blastoid features. Patients with DH/TH lymphoma often have advanced stage disease and a poor prognosis. HGBCL that lacks DH/TH genetics have similar, aggressive morphological features (Ok 2020).

Survival:

Overall survival (OS) for newly diagnosed DLBCL patients approaches 75% at 5 years; however, in high-risk patients, it may be as low as 25% to 30% (DH/TH, non-germinal center b-cell) to 50% (International Prognostic Index [IPI] 3 to 5) at 5 years (Culpin 2013, Cunningham 2013, Ziepert 2010). Among 202 patients aged 60 to 80 years old who were randomized to receive R-CHOP for DLBCL, the median OS was 8.4 years (Coiffier 2010).

After the introduction of the standard IPI, the use of the revised (R)-IPI has been proposed based on data from DLBCL patients treated with R-CHOP. The R-IPI is a better predictor of outcome than the standard IPI for patients with DLBCL treated with R-CHOP. The R-IPI includes the same factors as the IPI, but only includes 3 risk groups: very good (0 factors),

good (1 to 2 factors), and poor (3 to 5 factors); with a 5-year survival of 93%, 81%, and 61%, respectively (Ruppert 2020, Sehn 2007).

In a population-based study in the UK, the 5-year OS and RS (in DLBCL, NOS diagnosed 2004 to 2012 and followed through to 2014) was 46.6 (95% confidence interval [CI], 44.4 to 48.7) and 55.0 (52.6 to 57.4), respectively. Among the patients that received intensive first-line chemotherapy with curative intent, the 5-year OS was 58.5% (Smith 2015a).

In a study from the Netherlands, the 5-year RS of adult patients diagnosed with DLBCL between 2011 and 2018 decreased by age and stage. For stage 1, the 5-year RS was 96% in those 20 to 64 years of age, 84% in those 65 to 74 years of age, and 67% in those ≥ 75 years of age. For stage 2 to 4, the 5-year RS was 75% in those 20 to 64 years of age, 60% in those 65 to 74 years of age, and 46% in those ≥ 75 years of age (Durmaz 2022).

In the US, the 5-year RS was similar for males and females (64%), higher in whites than blacks (65.1% and 60.7%, respectively), and decreased with age (79.4% in those < 55 years of age, 70.6% in those 55 to 64, and 54.8% in those ≥ 65) (National Cancer Institute 2022a). By stage, the 5-year RS was 79.5%, 74.6%, 65.5%, 54.7% for stage 1, 2, 3, 4, respectively.

In a pooled analysis of outcomes of refractory DLBCL from 2 multi-country Phase 3 clinical trials (Lymphoma Academic Research Organization-CORAL and Canadian Cancer Trials Group LY.12) and 2 observational cohorts (MD Anderson Cancer Center and University of Iowa/Mayo Clinic Lymphoma Specialized Program of Research Excellence), the median OS was 6.1 (95% CI, 5.2 to 7.0) months in patients who received at least 3 lines of therapy. 1-year and 2-year survival rates were 26% and 17%, respectively (Crump 2017).

In a multicenter retrospective review of 124 patients with newly diagnosed PMBCL between 2001 and 2016, the 5-year OS for patients receiving R-CHOP, DA-EPOCH-R, and R-CHOP + RT were 76.1% (95% CI, 57.1% to 87.3%), 93.9% (95% CI, 77.8% to 98.4%), and 96.9% (95% CI, 79.8% to 99.5%), respectively (Chan 2019). Among patients with R/R PMBCL who received pembrolizumab, the median OS was 31.4 months (Armand 2019).

A clinical outcome analysis of 71 patients (60 patients had de-novo DH/TH and 11 had transformation of a previously diagnosed low-grade lymphoma) showed that the median OS was 17.7, 13.5, 12.3 months in patients treated with R-CHOP, R-EPOCH, R-HyperCVAD, respectively. Patients with DH/TH at transformation of previously diagnosed low-grade lymphoma had a very poor outcome (median OS = 10.8 months), which was inferior to patients with de-novo DH/TH (P = 0.0069). The OS for the entire cohort at 5 years was 48% (Habermann 2016).

Important co-morbidities:

Several studies have published details about comorbid conditions among patients diagnosed with DLBCL. Cohorts that included younger patients or were restricted to patients who were

treated with curative intent reported a lower prevalence of comorbidities. The most common comorbidities include diabetes, cardiovascular disease, hypertension, cerebrovascular disease, pulmonary disease, peptic ulcer disease, renal disease, solid tumor, arrythmia, and peripheral vascular disease. Other comorbidities include congestive heart failure, heart valve disease, myocardial infarct, psychiatric disorders, connective tissue/rheumatologic disease, and liver disease (Kobayashi 2011, Kocher 2020, Nabhan 2011, van de Schans 2012, Wästerlid 2019, Wieringa 2014).

Indication: Follicular lymphoma (FL) Grade 1-3A

Treatment of adult patients with R/R FL after 2 or more lines of systemic therapy.

Incidence:

FL is an indolent form of NHL that arises from B-lymphocytes and accounts for 20% to 30% of NHL (Monga 2019, Solal-Céligny 2010).

EU

The incidence of FL (including grades 1-3B) in the EU-27 for 2020 was estimated by multiplying the incidence of NHL in the EU-27 for 2020 (18.3/per 100,000, age standardized rate [European new]) by the proportion of FL in NHL from HMRN (19.3%) [(ECIS - European Cancer Information System)]. The estimated incidence of FL was 3.5 (3.9 in males and 3.3 in females) per 100,000 for 2020.

US

Based on the Surveillance, Epidemiology, and End Results (SEER) Program and Cancer Statistics Review, the age-adjusted incidence of FL in the US from 2016-2020 was 2.5 per 100,000 per year (2.7 in males and 2.3 in females) (National Cancer Institute 2022b). The percent of new cases by age group (45-54, 55-64, 65-74, 75-84, 85+) was 15.9%, 27.1%, 27.8%, 15.6%, and 4.9%, respectively (National Cancer Institute 2022a).

Prevalence:

EU

According to the Orphanet Report Series, the estimated FL prevalence in Europe (age-adjusted to the European population) was 3.7 per 10,000 (Orphanet Report Series 2022).

The prevalence of FL in the EU has been estimated as 4.8 to 4.9 per 10,000 in recent years (European Medicines Agency 2022a, European Medicines Agency 2022b, European Medicines Agency 2022d).

US

The prevalence of FL in the US was estimated by multiplying the annual FL incidence in the US derived from the SEER Program (2.5 per 100,000; 8,286 new cases per year) by the estimated disease duration (overall survival [OS], 13 or 15 years) The resulting prevalence estimates range from 3.25 per 10,000 to 3.75 per 10,000 using 13 or 15 years, respectively (National Cancer Institute 2022a).

Demographics of the target population:

FL rates are slightly higher for females in the UK while FL was more common in males in the US. FL incidence increases rapidly with age (Haematological Malignancy Research Network (HMRN)). Median age at diagnosis is 60-65 years and is most frequently diagnosed among those in their late 60s and early 70s (Ma 2012, National Cancer Institute 2022a). Incidence was highest in non-Hispanic whites followed by Hispanics of all races, non-Hispanic blacks, American-Indian/Alaskan natives, and Asians or Pacific Islanders, respectively (Cerhan 2020).

Risk Factors:

The etiology of FL is still poorly understood although many potential risk factors are similar to DLBCL. Risk is higher among older people and Caucasians, however, risk by sex varies by region (National Cancer Institute 2022a) (Haematological Malignancy Research Network (HMRN) , Ma 2012). Other potential risk factors include t(14;18) translocation, family history of NHL, genetic susceptibility loci (6p21.32), DRβ1 multiallelic amino acids at positions 11, 13, 28, and 30, 11q23.3 (near CRCX5), 11q24.3 (near ETS1), 3q28 (in LPP), 18q21.33 (near BCL2), and 8q24.21 (near PVT1); tumor necrosis factor receptors (sCD30, sCD27), Hepatitis C virus (HCV), autoimmune disorders (Sjögren's syndrome, rheumatoid arthritis, autoimmune hemolytic anemia, and aplastic anemia), hormonal therapy, environmental exposures (pesticides and permanent/dark-colored hair dyes), and increased BMI (in young adults) (Cerhan 2020).

The main existing treatment options:

The most frequently used first-line FL therapies include an anti-CD20 (rituximab or obinutuzumab) combined with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone), or bendamustine.

Treatment of R/R FL is influenced by previous treatment regimens, duration of remission, and other factors. Several treatment options are approved for R/R FL, including combination chemotherapy plus an anti-CD20 monoclonal antibody (rituximab [(Leonard 2019)] or obinutuzumab [(Sehn 2016]), radioimmunotherapy (ibritumomab tiuxetane [(Witzig 2002)]), immunomodulatory drugs (axicabtagene ciloleucel [(Jacobson 2022)] and mosunetuzumab [(budde LE 2021)]), and targeted therapies (copanlisib [(Dreyling 2020)] and tazemetostat [(Morschhauser 2020)]), although none are considered curative. Limitations with existing

therapies include the waiting period for CAR T-cell manufacturing, restricted availability, logistical challenges for radioimmunotherapy, observed toxicities, and route of administration.

Natural history of the indicated disease/condition in the untreated population, including mortality and morbidity:

Diagnosis is based on a surgical specimen/excisional lymph node biopsy. Histological grading of lymph node biopsies is carried out according to the average number of centroblasts/high-power field. The histological report provides a diagnosis according to the current WHO classification (Dreyling 2021). FL grade 3B is considered an aggressive lymphoma, whereas Grades 1, 2, and 3A are considered indolent diseases.

A staging system that is commonly used for adult NHL is the Ann Arbor staging system. Follicular Lymphoma International Prognostic Index (FLIPI) 1, revised FLIPI called FLIPI 2, and PRIMA prognostic index risk factors are used for prognostic purposes (Dreyling 2021).

Bone marrow involvement occurs in approximately 70% of patients and is characterized by paratrabecular lymphoid aggregates (Freedman 2020).

Most patients with FL present with advanced stage disease at diagnosis, however, many early and advanced stage FL do not require immediate treatment unless they have certain symptoms (symptomatic nodal disease, compromised end organ function, symptomatic extranodal disease, or cytopenias) (Freedman 2020). Due to the indolent nature of FL, patients with limited or asymptomatic disease can be monitored under close observation. Treatment will not be required for 50% of asymptomatic patients at 3 years and 20% at 10 years. The estimated OS is likely higher than 80% at 10 years among those treated with rituximab chemotherapy (Cartron 2022). After first relapse/progression, the median OS for patients on second-line treatment is greater than 10 years (Batlevi 2020). However, those experiencing progression within 24 months after treatment initiation (POD24) had worse prognoses with a 5-year survival of 50% (Casulo 2015). Patients classified as double refractory experience substantially shorter time to successive lines of therapy, higher rates of histological transformation, and shorter OS compared to patients who were not double refractory (Salles 2022).

Histological transformation to an aggressive lymphoma occurs in 2% to 3% of patients per year; 25–35% of patients (Swerdlow 2017). Transformation results in rapid progression of extranodal disease, hypercalcemia, elevated serum lactate dehydrogenase, and lymphadenopathy (Kridel 2012, Montoto 2007). For patients who undergo histological transformation, median survival is around 4 to 5 years and likely shorter among those with transformation in the first year (Sarkozy 2016).

Given that with each progression or relapse the disease tends to become more refractory, risk of transformation increases, and most patients eventually succumb to their disease. Due to

the limitations of existing therapies, an unmet medical need exists in R/R FL. Novel treatment is needed to fulfill this unmet medical need.

Survival:

While FL remains incurable, improvements in treatment and detection have resulted in improvements in overall survival (OS). OS for newly diagnosed and lower grade FL has been observed at around 90% at 5 years and 70-80% at 10 years (Batlevi 2020, Rajamäki 2022).

In a population-based cancer registry study from Sweden, the median overall survival (mOS) was calculated to be 71.4 months (~6 years) in patients diagnosed from 1993-1999 among diffuse, centroblastic, or not otherwise specified FL (Ji 2009). Another study utilizing the Swedish Lymphoma Registry reported OS by 3 distinct calendar periods of disease diagnosis (2000-2002, 2003-2007, and 2008-2010). The mOS was 10 years for the 2000-2002 cohort, however, mOS was not reached in the 2 latter cohorts at the time of the study (Junlén 2015).

In the Netherlands, one study presented an mOS of 5.8 years based on a registry of Dutch patients diagnosed with FL between 1981-1989. The 5-year OS and 10-year OS rates were 54% and 26%, respectively (Krol 2003).

A study in France found an mOS of 13 years utilizing a French registry of patients diagnosed from 1980-2009. Comparing the 1980-1989 and 2000-2009 periods, the 5-year net survival increased from 58% to 70% (Dandoit 2015).

In Slovenia, FL patients treated at the Institute of Oncology and other Slovene hospitals between 2000 and 2010 found a mOS of 9.4 years among those treated with systemic therapy. The overall patient group did not reach mOS. 5-year and 10-year OS rates for the study were 77% and 53%, respectively (Južnič Šetina 2015).

In the US, the 5-year relative survival was 90.6% and was similar between males (89.8%) and females (91.4%). 5-year RS decreased with increasing age (95.3% for < 55 years, 93.1% for 55-64, and 86.4% for 65+). By stage, the 5-year RS was 97.1%, 91.6%, 89.4%, and 85.8% for stages 1, 2, 3, 4, respectively (National Cancer Institute 2022a).

Important co-morbidities:

Among patients with FL, common comorbidities include hypertension, cardiovascular disease, atrial fibrillation, diabetes, autoimmune disorders, gastrointestinal disorders (Crohn's disease, ulcerative colitis), liver disease, thyroid disease, HIV, and pulmonary disease (COPD or asthma) (Becnel 2018, Mihaljevic 2016, Nabhan 2012). Additionally, comorbid conditions that contain similar symptoms as FL such as diabetes, congestive heart failure, and chronic obstructive pulmonary disease can lead to delayed diagnosis (Smith 2021).

Module SII Non-Clinical Part of the Safety Specification

The nonclinical safety package to support the market approval of epcoritamab consists of in vitro cross-species binding assessments, in vitro safety studies using human cells and tissues (cytokine release assay, cross-reactivity, hemolytic potential, and plasma compatibility assays), and in vivo studies in cynomolgus monkeys by both intravenous (IV) and SC administration route (including safety pharmacology and local tolerance evaluations).

The primary toxicity findings in cynomolgus monkeys administered epcoritamab included adverse clinical signs (incidents of vomiting, decreased activity, hunched posture; and mortality [≥ 1 mg/kg]). These findings were considered associated with elevated cytokine levels, observed primarily following the first dose. SC administration of epcoritamab to cynomolgus monkeys was associated with lower maximum concentration values and lower peak cytokine levels, but comparable B-cell depletion relative to the same IV dose (mg/kg). A priming dose administered IV as a lower dose than a later dose was associated with lower cytokine levels. Other epcoritamab related findings included reversible hematologic changes (alterations in leukocytes and lymphocytes), and reversible B-cell depletion in peripheral blood consistent with reversible decreases in lymphoid cellularity in lymphoid tissues observed microscopically.

There were no epcoritamab-related local tolerance findings, nor any identified adverse effects on the cardiovascular, respiratory, and neurological systems, following IV and SC administration of epcoritamab in cynomolgus monkeys.

Consistent with the in vivo findings in cynomolgus monkeys, epcoritamab also induced cytokine release in an in vitro cytokine release assay using human whole blood. In an in vitro assay of hemolytic potential using human whole blood, epcoritamab did not cause hemolysis and was also compatible with human whole blood and plasma at concentrations ≤ 20 µg/mL. In the good laboratory practice (GLP) tissue cross-reactivity study using a comprehensive panel of human and cynomolgus monkey tissues, binding of epcoritamab was comparable across species and limited to mononuclear cells in various tissues. As CD3 and CD20 are expressed on T cells and B cells, respectively, the staining of blood lymphocyte and mononuclear cells in a majority of the tissues was in line with expected reactivity.

Overall, the observed toxicity findings in vivo are consistent with the anticipated pharmacologic activity of epcoritamab.

Key Safety Findings (from Non-Clinical Studies)	**Relevance To Human Usage**
Toxicity	
Acute and repeat dose toxicity Effects generally consistent with the pharmacologic mechanism of action of epcoritamab were observed in cynomolgus monkeys. These findings included dose-related adverse clinical signs (including vomiting, decreased activity, and mortality [at high doses ≥ 1 mg/kg]) and cytokine release; reversible hematologic alterations in total leukocyte and lymphocyte counts; reversible B-cell depletion in peripheral blood; and reversible decreased lymphoid cellularity in secondary lymphoid tissues.	Because the findings observed in the toxicology studies were consistent with the mechanism of action of epcoritamab, these are anticipated to occur or be observed in humans.
Reproductive toxicity Animal fertility and embryofetal development studies have not been conducted with epcoritamab, however, epcoritamab did not cause toxicological changes in the reproductive organs of male or female cynomolgus monkeys at doses up to 1 mg/kg/week in the IV general toxicity study of 5-week duration.	Epcoritamab has the potential to be transmitted from the pregnant mother to the developing fetus, and based on its mechanism of action, in utero exposure to epcoritamab may cause adverse outcomes including B-cell lymphocytopenia and alterations in normal immune responses.
Developmental toxicity No developmental toxicity studies have been conducted.	The risk of developmental toxicity in humans is unknown.
Nephrotoxicity Nephrotoxicity was not observed after IV or SC administration in cynomolgus monkeys in toxicity studies of up to 5-week duration.	Based on studies in non-human primates, nephrotoxicity is not anticipated in humans.
Hepatotoxicity Hepatotoxicity was not observed after IV or SC administration in cynomolgus monkeys in general toxicity studies up to 5-weeks duration.	Based on studies in non-human primates, hepatotoxicity is not anticipated in humans.
Genotoxicity Genotoxicity studies were not conducted for epcoritamab. Genotoxicity studies are routinely conducted for pharmaceuticals but are not applicable to biotechnology-derived pharmaceuticals, because it is not expected that these substances would interact directly with DNA or other chromosomal material.	It is not expected that large molecules like epcoritamab would interact directly with DNA or chromosomal material. Thus, no genotoxic effect is expected after administering epcoritamab to human subjects.

Key Safety Findings (from Non-Clinical Studies)	**Relevance To Human Usage**
Carcinogenicity Carcinogenicity studies are generally not relevant for biopharmaceuticals including monoclonal antibodies and related products, nor required for oncology agents intended for treatment of advanced systemic disease. Moreover, epcoritamab has no known action related to the cell cycle and is not expected to have any action which influences DNA integrity.	Carcinogenicity studies have not been conducted with epcoritamab. No carcinogenic effect is expected after administering epcoritamab to human subjects.
Safety Pharmacology	
Cardiovascular Electrocardiography and heart rate measurements were included in the GLP monkey study, with no epcoritamab-related findings noted in these evaluations.	Based on studies in non-human primates, no clinically meaningful cardiovascular toxicity is anticipated in humans.
Nervous system To evaluate potential adverse effects the central nervous system (CNS) detailed clinical observations following IV and SC dosing was included in the cynomolgus monkey toxicity study. There were no direct epcoritamab-related adverse effects on the neurological systems following administration of epcoritamab in cynomolgus monkeys.	Consistent with the mechanism of action of epcoritamab, ICANS is an important identified risk for epcoritamab, and neurological events is an identified risk for epcoritamab.
Other systems (dependent on the product's pharmacological activity)	None known at this time.
Mechanisms for drug interactions Epcoritamab can cause transient release of cytokines that may potentially suppress CYP450 enzymes. No formal drug interaction studies have been conducted with epcoritamab.	The elevations of specific pro‐inflammatory cytokines observed after the epcoritamab injections are transient and modest in nature and attenuate with repeat dosing. The transient release of cytokines may potentially suppress CYP enzymes.

Key Safety Findings (from Non-Clinical Studies)	Relevance To Human Usage
Local Tolerance The local tolerance of epcoritamab drug substance was assessed as part of the pivotal GLP toxicity study in monkeys. No separate studies were performed. Examination of the IV infusion sites and the SC injection sites revealed no significant epcoritamab-related clinical or microscopic signs of local irritation. The vehicle for IV administration was 0.9% saline and for SC administration 30 mM acetate buffer at pH 5.5 with 150 mM sorbitol. The clinical epcoritamab SC formulation contains 30 mM sodium acetate, 150 mM sorbitol, 0.04% polysorbate 80, pH 5.5.	Injection site reaction is an identified risk for epcoritamab.

Non-Clinical Safety Findings that are Included as Safety Concerns

Safety Concerns	
Important identified risks	CRS and ICANS
Important potential risks	None
Missing information	None

Based on findings in non-clinical studies and epcoritamab mechanism of action, Cytokine Release Syndrome (CRS) and Immune Effector cell-associated neurotoxicity syndrome (ICANS) were anticipated in humans and are important identified risks.

Module SIII Clinical Trial Exposure

The core safety analysis of DLBCL is based on the pivotal GCT3013-01 trial, which provides the largest population from a single arm trial. Data from the Dose Escalation and Expansion Part were pooled for subjects who were assigned to receive the 48 mg dose regimen and received at least one dose of epcoritamab, resulting in an analysis set of 167 subjects with R/R LBCL (the primary safety analysis pool), comprising 148 subjects with R/R DLBCL and 19 subjects with non-DLBCL subtypes. The safety discussions throughout the RMP are based on the 167 subjects with R/R LBCL from the primary safety analysis pool.

The core safety analysis of FL (1-3A) is based on the pivotal GCT3013-01 trial in the Dose Escalation and Expansion Part for subjects who were assigned to receive the 48 mg dose regimen utilizing the 2-step SUD regimen (0.16/0.8/48 mg) and received at least one dose of epcoritamab, resulting in an analysis set of 129 subjects with R/R FL (1-3A).

The 2-step SUD regimen for epcoritamab was initially developed to treat subjects with R/R FL, an indolent disease. The FL 3-step SUD regimen was later developed for epcoritamab (0.16/0.8/3/48 mg) to further reduce the incidence and severity of CRS observed in the 2-step SUD regimen in subjects with R/R FL. Safety data from the Optimization Part (Arm A) of the GCT3013-01 trial for R/R FL subjects receiving the 3-step SUD regimen for epcoritamab are presented.

Epcoritamab exposure data from clinical studies for R/R LBCL and R/R FL are presented in Table 2, Table 3, Table 4, Table 5, Table 6.

Table 2. Duration of Exposure (All R/R LBCL and R/R FL Treated Patients)

	GCT3013-01 ESC + EXP			
	R/R LBCL (N = 167)		R/R FL (N = 129)	
Duration of Exposure	Patients	Person-Time (PY)	Patients	Person-Time (PY)
≥ 1 Day	167	78.5	129	104.1
≥ 4 Weeks	145	77.7	125	104.0
≥ 12 Weeks	101	71.7	105	100.9
≥ 24 Weeks	68	61.0	79	92.9
≥ 36 Weeks	52	51.6	66	85.8
≥ 48 Weeks	30	34.3	51	74.4
≥ 60 Weeks	14	18.2	37	59.6
≥ 72 Weeks	4	6.2	28	48.4
≥ 84 Weeks	2	3.3	17	32.3
≥ 96 Weeks	0	0	6	13.2
Total	167	78.5	129	104.1

ESC = Escalation; EXP = Expansion; FL = Follicular lymphoma; LBCL = Large B-cell lymphoma; PY = Patient years; R/R = Relapsed/refractory

Study GCT3013-01: Data cutoff date for R/R LBCL - 31JAN2022; Data cutoff date for R/R FL - 21APR2023.

Patients who received at least 1 dose of epcoritamab and were assigned to receive the 48 mg dose are included.

Person-time is calculated as the sum of exposure to epcoritamab for all Patients within category divided by 365.25.

Table 3. Exposure by Age Group and Gender (All R/R LBCL and R/R FL Treated Patients)

Analysis Set (N)	Patients			Person-Time (PY)		
Age Group (Years)	Male	Female	Total	Male	Female	Total
GCT3013-01 ESC + EXP R/R LBCL (N = 167)						
<45	7	9	16	1.4	4.5	5.9
45 - <65	45	22	67	18.1	10.3	28.3
65 - <75	33	20	53	15.8	10.7	26.5
75 - <85	19	12	31	10.9	6.9	17.8
≥ 85	0	0	0	0	0	0
Total	104	63	167	46.2	32.3	78.5
GCT3013-01 ESC + EXP R/R FL (N = 129)						
<45	4	2	6	3.9	1.7	5.5
45 - <65	38	18	56	29.7	10.8	40.6
65 - <75	26	24	50	24.0	22.6	46.6
75 - <85	12	5	17	6.6	4.7	11.4
≥ 85	0	0	0	0	0	0
Total	80	49	129	64.2	39.9	104.1

ESC = Escalation; EXP = Expansion; FL = Follicular lymphoma; LBCL = Large B-cell lymphoma; PY = Patient years; R/R = Relapsed/refractory

Studies GCT3013-01. Data cutoff date for R/R LBCL: 31JAN2022; Data cutoff date for R/R FL - 21APR2023.

Patients who received at least 1 dose of epcoritamab and were assigned to receive the 48mg dose are included.

Person-time is calculated as the sum of exposure to epcoritamab for all patients within category divided by 365.25.

Table 4. Exposure by Ethnic Origin (All R/R LBCL and R/R FL Treated Patients)

	GCT3013-01 ESC + EXP			
	R/R LBCL (N = 167)		R/R FL (N =129)	
Ethnic Origin	Patients	Person-Time (PY)	Patients	Person-Time (PY)
White	106	47.2	77	56.3
Asian	30	14.9	7	8.2
Black or African American	0	0	0	0
Native Hawaiian or Other Pacific Islander	1	0.2	0	0
American Indian or Alaska Native	0	0	0	0
Other	6	3.1	2	0.5
Not Reported	24	13.2	43	39.1
Total	167	78.5	129	104.1

ESC = Escalation; EXP = Expansion; FL = Follicular lymphoma; LBCL = Large B-cell lymphoma; PY = Patient years; R/R = Relapsed/refractory

Study GCT3013-01: Data cutoff date for R/R LBCL - 31JAN2022; Data cutoff date for R/R FL - 21APR2023.

Asian includes Asian Indian, Chinese, Japanese, Malay, and Asian Other.

Patients who received at least 1 dose of epcoritamab and were assigned to receive the 48mg dose are included.

Person-time is calculated as the sum of exposure to epcoritamab for all patients within category divided by 365.25.

Table 5. Exposure by Baseline Renal Function (All R/R LBCL and R/R FL Treated Patients)

	GCT3013-01 ESC + EXP			
	R/R LBCL (N = 167)		R/R FL (N =129)	
Renal Function at Baseline	**Patients**	**Person-Time (PY)**	**Patients**	**Person-Time (PY)**
Normal	70	31.8	53	41.9
Mild Impairment	69	34.0	54	43.8
Moderate Impairment	25	12.1	22	18.5
Severe Impairment	0	0	0	0
Unknown	3	0.7	0	0
Total	167	78.5	129	104.1

CrCl = Creatinine clearance; ESC = Escalation; EXP = Expansion; FL = Follicular lymphoma; LBCL = Large B-cell lymphoma; PY = Patient years; R/R = Relapsed/refractory

Study GCT3013-01: Data cutoff date for R/R LBCL - 31JAN2022; Data cutoff date for R/R FL - 21APR2023.

Patients who received at least 1 dose of epcoritamab and were assigned to receive the 48mg dose are included.

Person-time is calculated as the sum of exposure to epcoritamab for all patients within category divided by 365.25.

Patients are classified based on estimated creatinine clearance using the Cockcroft-Gault method (Normal: CrCl ≥ 90 mL/min; Mild: 60 mL/min ≤ CrCl < 90 mL/min; Moderate: 30 mL/min ≤ CrCl < 60 mL/min; Severe: CrCl < 30 mL/min).

Table 6. Exposure by Baseline Hepatic Function (All R/R LBCL and R/R FL Treated Patients)

	GCT3013-01 ESC + EXP			
	R/R LBCL (N = 167)		R/R FL (N=129)	
Hepatic Function at Baseline	**Patients**	**Person-Time (PY)**	**Patients**	**Person-Time (PY)**
Normal	132	60.8	108	87.9
Mild Impairment	30	15.7	21	16.2
Moderate Impairment	1	0.7	0	0
Severe Impairment	0	0	0	0
Unknown	4	1.4	0	0
Total	167	78.5	129	104.1

AST = Aspartate aminotransferase; ESC = Escalation; EXP = Expansion; FL = Follicular lymphoma; LBCL = Large B-cell lymphoma; PY = Patient years; R/R = Relapsed/refractory; TBIL = Total bilirubin; ULN = Upper limit of normal

Study GCT3013-01: Data cutoff date for R/R LBCL - 31JAN2022; Data cutoff date for R/R FL - 21APR2023.

Patients who received at least 1 dose of epcoritamab and were assigned to receive the 48mg dose are included.

Person-time is calculated as the sum of exposure to epcoritamab for all patients within category divided by 365.25.

Patients are classified based on the National Cancer Institute Organ Dysfunction Working Group (NCI-ODWG) (Normal: TBIL ≤ ULN and AST ≤ ULN; Mild: TBIL ≤ ULN and AST > ULN or ULN < TBIL ≤ 1.5 × ULN; Moderate: 1.5 × ULN < TBIL ≤ 3 × ULN; Severe: TBIL > 3 × ULN).

Module SIV Populations Not Studied in Clinical Trials

SIV.1 Exclusion Criteria in Pivotal Clinical Studies Within the Clinical Development Program

LBCL/DLBCL -specific:

Criterion 1: Subject with creatinine clearance < 45 mL/min and GFR < 45 mL/min/1.73 m^2.
Reason for exclusion: Patients with severe renal impairment were excluded to limit confounding the interpretation of safety findings.
Is it considered to be included as missing information?: No
Rationale: The safety profile in subjects with severe renal impairment has not been established at this time and additional pharmacovigilance activities are not planned in this patient population.

Criterion 2: Subject who has undergone allogenic stem cell transplantation (allo-SCT)
Reason for exclusion: Excluded to limit confounding the interpretation of safety findings.
Is it considered to be included as missing information?: No
Rationale: Clinicians should determine whether the benefit of treatment outweighs the risks for an individual patient.

FL specific:

Criterion 1: Subject with creatinine clearance < 45 mL/min for FL
Reason for exclusion: Patients with severe renal impairment were excluded to limit confounding the interpretation of safety findings.
Is it considered to be included as missing information?: No
Rationale: The safety profile in subjects with severe renal impairment has not been established at this time and additional pharmacovigilance activities are not planned in this patient population.

All Indications:

Criterion 1: Subject less than 18 years of age
Reason for exclusion: Standard precautionary measure for clinical trials due to unknown effect on pediatric subjects.
Is it considered to be included as missing information?: No
Rationale: Pediatric subjects are not included in the current population indication. Use in pediatric subjects is being evaluated in the clinical development program.

Criterion 2: Subject with primary CNS lymphoma or known CNS involvement
Reason for exclusion: Patients with primary CNS lymphoma or known CNS involvement were excluded to limit confounding the interpretation of safety findings.
Is it considered to be included as missing information?: No
Rationale: The safety profile in subjects with primary CNS lymphoma or known CNS involvement has not been established at this time. Clinicians should determine whether the benefit of treatment outweighs the risks for an individual patient.

Criterion 3: Subject with AST or ALT >3 × ULN. Subject with total bilirubin >1.5 × ULN
Reason for exclusion: Patients with moderate or severe hepatic impairment were excluded to limit confounding the interpretation of safety findings
Is it considered to be included as missing information?: No
Rationale: The safety profile in subjects with moderate and severe hepatic impairment has not been established at this time and additional pharmacovigilance activities are not planned in this patient population.

Criterion 4: Subject with clinically significant cardiovascular disease
Reason for exclusion: Patients with clinically significant cardiovascular disease at baseline were excluded to limit confounding the interpretation of safety findings.
Is it considered to be included as missing information?: No
Rationale: Clinicians should determine whether the benefit of treatment outweighs the risks for an individual patient.

Criterion 5: Subject with chronic ongoing infectious disease(s)
Reason for exclusion: Patients with chronic ongoing infectious disease(s) at baseline were excluded to prevent potential worsening of the infection due to epcoritamab.
Is it considered to be included as missing information?: No
Rationale: Clinicians should determine whether the benefit of treatment outweighs the risks for an individual patient.

Criterion 6: Subject with confirmed history or current autoimmune disease or other diseases resulting in permanent immunosuppression or requiring permanent immunosuppressive therapy. Subject with known positive HIV.
Reason for exclusion: Patients were excluded to prevent potential increased risk of infections.
Is it considered to be included as missing information?: No
Rationale: Anticipated epcoritamab mechanism-based lymphopenia and use of systemic corticosteroids may increase the risk of infections. Clinicians should determine whether the benefit of treatment outweighs the risks for an individual patient.

Criterion 7: Subject with seizure disorder(s) requiring therapy
Reason for exclusion: Patients were excluded to limit confounding the interpretation of safety findings.
Is it considered to be included as missing information?: No
Rationale: Clinicians should determine whether the benefit of treatment outweighs the risks for an individual patient.

Criterion 8: Subject who has received prior therapy with an investigational bispecific antibody targeting CD3 and CD20
Reason for exclusion: Excluded to limit confounding the assessment of efficacy and safety.
Is it considered to be included as missing information?: No
Rationale: Clinicians should determine whether the benefit of treatment outweighs the risks for an individual patient.

Criterion 9: Female subject with positive result(s) for pregnancy. Female who is breast-feeding. Woman of reproductive/childbearing potential.
Reason for exclusion: Standard precautionary measure for clinical trials due to non-clinical findings and unknown effects in pregnant and/or lactating patients.
Is it considered to be included as missing information?: No
Rationale: The safety profile in subjects who are pregnant or breast feeding is unknown at this time. Given the demographics of the target population, use is anticipated to be low in this patient population. Clinicians should verify pregnancy status and inquire about breast feeding before administering epcoritamab in females of reproductive/childbearing potential. Epcoritamab is not recommended during pregnancy and in women of childbearing potential not using contraception. Breast-feeding should be discontinued during treatment with epcoritamab and for at least 4 months after the last dose.

SIV.2 Limitations to Detect Adverse Reactions in the Clinical Development Program

The clinical development program is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

SIV.3 Limitations in Respect to Populations Typically Under Represented in Clinical Development Program

Table 7. Exposure of Special Populations Included or Not in the Clinical Development Program

Type of special population	Exposure
Pregnant and breastfeeding women	No pregnant or lactating patients have been exposed to epcoritamab.
Patients with moderate or severe hepatic impairment	Epcoritamab has not been studied in patients with severe hepatic impairment and data are limited in patients with moderate hepatic impairment. None of the treated subjects from Studies GCT3013-01 and GCT3013-04 were classified with severe hepatic dysfunction at baseline. Only 1 subject had moderately impaired hepatic function at baseline.
Patients with severe renal impairment	Epcoritamab has not been studied in patients with severe renal impairment to end stage renal disease. None of the treated subjects from Studies GCT3013-01 and GCT3013-04 were classified with severe renal impairment at baseline.
HIV/Immunocompromised patients	Epcoritamab has not been studied in HIV/immunocompromised patients.
Patients with clinically significant cardiovascular disease	Epcoritamab has been studied in a limited number of subjects with clinically significant cardiovascular disease.
Pediatric Patients (≤ 18 years old)	Epcoritamab has not been studied in pediatric patients.
History or presence of clinically relevant CNS pathology	Epcoritamab has not been studied in patients with a history or presence of clinically relevant CNS pathology.
Population with relevant different ethnic origin	Subject populations in clinical trials included patients with a variety of racial and ethnic backgrounds, but predominantly in White and Not Hispanic or Latino populations (Table 4).

CNS = Central Nervous System; HIV = Human immunodeficiency virus

Module SV Post-Authorization Experience

SV.1 Post-Authorization Exposure

Since the approval of epcoritamab for R/R DLBCL and high-grade B-cell lymphoma in the US in May 2023, and subsequent approvals in the European Union, Japan, United Arab Emirates, and

Kuwait, global post-marketing exposure has begun to accrue. As of 22 September 2023, approximately 565 patients have been treated with epcoritamab in the post-marketing setting (data on file).

Module SVI Additional EU Requirements for the Safety Specification

Potential for Misuse for Illegal Purposes

Epcoritamab will be distributed commercially as a concentrate for solution and a solution to be given as a SC injection by health care professionals (HCPs). It does not have addictive properties. The potential for misuse for illegal purposes is low.

Module SVII Identified and Potential Risks

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

SVII.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Reasons for not including an identified or potential risk in the list of safety concerns in the RMP:

Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):

Not applicable

Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated:

Tumor lysis syndrome (TLS)

TLS was observed in clinical trials with epcoritamab. The observed frequency of TLS events in the epcoritamab clinical program was low.

LBCL/DLBCL: For LBCL subjects in the pivotal study, 3 (1.8%) subjects experienced a treatment-emergent adverse event (TEAE) of TLS. All 3 events met the criteria for Clinical TLS (CTLS), were grade 3, and were considered treatment related. One event resolved and the other 2 events were ongoing at the time of death due to disease progression.

FL: No FL subjects in the pivotal study receiving the epcoritamab 2-step SUD regimen had events of TLS.

TLS commonly occurs in hematological malignant patients particularly non-Hodgkin's lymphoma and acute leukemia due to chemotherapy or spontaneously. Hematologists and Oncologists treating hematological malignancies have appropriate awareness of this risk and follow standard prophylaxis and treatment as part of routine clinical practice. TLS risk is monitored via routine pharmacovigilance.

Known risks that require no further characterization and are followed up via routine pharmacovigilance and for which the risk minimization messages in the product information are adhered by prescribers (e.g., actions being part of standard clinical practice in each EU Member state where the product is authorized):

Neutropenia

Neutropenia is a very common TEAE observed in clinical trials with epcoritamab.

LBCL/DLBCL: For LBCL subjects in the pivotal study, neutropenia events (including febrile neutropenia) were reported in 47 (28.1%) subjects, with 36 subjects experiencing grade 3 or 4 events. Neutropenia was managed with G-CSF (15.0%) and/or dose delays (4.2%). No subjects discontinued epcoritamab treatment due to a TEAE of neutropenia.

FL: For FL subjects in the pivotal study receiving the 2-step SUD regimen, neutropenia events were reported in 36 (27.9%) subjects, with 32 subjects experiencing grade 3 or 4 events. Neutropenia was managed with G-CSF in 23 (63.9%) subjects. Eight (6.2%) subjects required dose delays and no subjects discontinued epcoritamab treatment due to a TEAE of neutropenia. Febrile neutropenia was reported in 4 (3.1%) subjects, all were grade 3 events. Of the 4 subjects with febrile neutropenia, 75% were managed with G-CSF. Four (3.1%) subjects required dose delays and no subjects discontinued epcoritamab treatment due to a TEAE of febrile neutropenia.

Hematologists and oncologists treating hematological malignancies have appropriate awareness of this risk and follow standard prophylaxis and treatment as part of routine clinical practice. Neutropenia risk is monitored via routine pharmacovigilance.

Neurological events (excluding ICANS)

Neurological events were observed in clinical trials with epcoritamab.

LBCL/DLBCL: Fifty nine of 167 (35.3%) subjects experienced neurological events. The most common neurological TEAEs (≥ 2% of subjects) were headache (12.6%; 21 subjects), ICANS (6.0%; 10 subjects), dizziness (5.4%; 9 subjects), paresthesia (3.6%; 6 subjects), tremor (3.6%; 6 subjects), and anxiety (2.4%; 4 subjects). Most of the events were nonserious and were grade 1 or 2 in severity.

FL: For FL subjects in the pivotal study receiving the 2-step SUD regimen, 62 (48.1%) subjects experienced neurological events using the broad definition. The most common neurological TEAEs (≥ 2% of subjects) were headache (19.4%; 25 subjects), dizziness (11.6%; 15 subjects), ICANS (6.2%; 8 subjects), paresthesia (4.7%; 6 subjects), anxiety (4.7%; 6 subjects), depression (3.1%; 4 subjects), balance disorder (2.3%; 3 subjects), lethargy (2.3%; 3 subjects), and tremor (2.3%; 3 subjects). Most of the events were nonserious and were grade 1 or 2 in severity.

Hematologists and Oncologists treating hematological malignancies have appropriate awareness of this risk and follow standard prophylaxis and treatment as part of routine clinical practice. Neurological events (excluding ICANS) risk is monitored via routine pharmacovigilance.

Known risks that do not impact the risk-benefit profile:

Injection site reactions

Injection site reactions after subcutaneous administration of epcoritamab is a very common TEAE observed in clinical trials with epcoritamab.

LBCL/DLBCL: For LBCL subjects in the pivotal study, 50 (29.9%) subjects experienced at least 1 TEAE of injection site reaction. In all subjects, the maximum event grade was either grade 1 (28.1%; 47 subjects) or grade 2 (1.8%; 3 subjects). No grade 3 or higher events were observed. Eleven (6.6%) subjects required treatment for at least 1 injection site reaction. Treatment generally consisted of topical steroids and/or oral antihistamines. None of the events resulted in dose modifications.

FL: For FL subjects in the pivotal study receiving the 2-step SUD regimen, 73 (56.6%) subjects experienced at least 1 TEAE of injection site reaction. In all subjects, the maximum event grade was either grade 1 (41.1%; 53 subjects) or grade 2 (15.5%; 20 subjects). No grade 3 or higher events were observed. Thirty-six (49.3%) subjects required treatment for at least 1 injection site reaction. Treatment generally consisted of topical steroids and/or oral antihistamines. Three (2.3%) subjects required dose delays and no subjects discontinued epcoritamab treatment due to a TEAE of injection site reaction.

Hematologists and Oncologists treating hematological malignancies have appropriate awareness of this risk and follow standard prophylaxis and treatment as part of routine clinical practice. Injection site reactions risk is monitored via routine pharmacovigilance.

Pyrexia

Pyrexia is a very common TEAE observed in clinical trials with epcoritamab. All TEAEs of pyrexia during the conduct of the trials were queried and confirmed by the Investigator to be considered as a fever of unknown etiology and not attributed to CRS.

LBCL/DLBCL: For LBCL subjects in the pivotal study, pyrexia of any grade occurred in 22.8% of subjects. No grade 3 or higher events were observed. Pyrexia led to dose delay in 3%.

FL: For FL subjects in the pivotal study receiving the 2-step SUD regimen, pyrexia of any grade occurred in 24.8% of subjects. In all subjects, the event of pyrexia was mostly Grade 1 or 2. The maximum event grade was reported as Grade 1 in 17.8%, Grade 2 in 4.7% and Grade 3 in 2.3% of subjects. No subjects had a grade 4 event of pyrexia. Pyrexia led to dose delay in 3.9% and no subjects discontinued epcoritamab treatment due to a TEAE of pyrexia.

Hematologists and Oncologists treating hematological malignancies have appropriate awareness of this risk and follow standard prophylaxis and treatment as part of routine clinical practice. Pyrexia risk is monitored via routine pharmacovigilance.

Other reasons for considering the risks not important:

Not applicable.

SVII.1.2 Risks Considered Important for Inclusion in the RMP

Important Identified Risks

Identified risk 1: Cytokine Release Syndrome (CRS)

Risk-benefit impact: CRS is a class effect for other bispecific anticancer therapies and drugs engaging with T-cells. Based on epcoritamab's mechanism of action, CRS is expected with epcoritamab. CRS has been observed with epcoritamab in clinical trials.

LBCL/DLBCL: In Study GCT3013-01, 2.4% (4/167) of LBCL subjects had grade 3 CRS. In Study GCT3013-01 + Study GCT3013-04, 4.0% (15/374) of All B-NHL subjects had grade 3 CRS. One (0.3%) subject in the All B-NHL group had grade 4 CRS. There were no grade 5 CRS events.

FL: In Study GCT3013-01, within the FL subjects receiving the 2-step SUD regimen, there was an overall incidence of CRS (grade 1-3) at 66.7% (86/129), with an occurrence of grade 3 CRS in 1.6% (2/129) subjects. There were no events of grade 4 or 5 CRS. CRS led to dose delay in 11.6% of subjects, and no subjects discontinued epcoritamab treatment due to a TEAE of CRS. All subjects with CRS recovered with a median time to recovery of 2.0 days.

The 3-step SUD regimen in the optimization cohort of Study GCT3013-01 has significantly mitigated the risks of CRS, exhibiting a 48.8% (42/86) incidence of Grade 1-2 CRS (39.5% [34/86] Grade 1 and 9.3% [8/86] Grade 2). There were no reports of Grade 3 or higher CRS events. Of the 42 subjects with Grade 1-2 CRS 38.1% of CRS events led to dose delay and no subjects discontinued epcoritamab treatment due to a TEAE of CRS.

Identified risk 2: Immune effector cell-associated neurotoxicity syndrome (ICANS)

Risk-benefit impact: ICANS is a class effect for other bispecific anticancer therapies and drugs engaging with T-cells. Based on epcoritamab's mechanism of action, ICANS is expected with epcoritamab. ICANS has been observed with epcoritamab in clinical trials.

LBCL: In Study GCT3013-01, 6.0% (10/167) of LBCL subject experienced ICANS with most of the events either grade 1 (4.2%; 7 subjects) or grade 2 (1.2%; 2 subjects) and no grade 3 or 4 events. One (0.6%) subject had a fatal ICANS event (grade 5).

FL: In Study GCT3013-01, 6.2% (8/129) of FL subjects receiving the 2-step SUD regimen experienced ICANS with most of the events either grade 1 (3.9%; 5 subjects) or grade 2 (2.3%; 3 subjects) and no grade 3 or higher events. ICANS led to dose delay in 0.8% and no subjects discontinued epcoritamab treatment due to a TEAE of ICANS. All subjects with ICANS recovered with a median time to recovery of 2.0 days.

The 3-step SUD regimen in the optimization cohort of Study GCT3013-01 has significantly mitigated the risk of ICANS. There were no reports of ICANS observed.

Identified risk 3: Serious Infections

Risk-benefit impact: Infections are among the most common, potentially serious complications of B-cell malignancies and their treatments, due to immunosuppression caused by the underlying malignancy and treatments. Infections have been reported with other bispecific antibody therapies. Epcoritamab can cause immunomodulation of B- and T-cell interactions, B-cell depletion, and subsequently hypogammaglobulinemia. Additionally, cytopenias observed during epcoritamab treatment may cause an increased risk of serious infections. Serious infections have been observed with epcoritamab in clinical trials.

LBCL: For LBCL, serious TEAEs of infection were reported in 16.2% (27/167) and fatal TEAEs in 2.4% (4/167) of subjects; all subjects were heavily pretreated and no fatal infection events were considered related to epcoritamab.

FL: For FL, serious TEAEs of infection were reported in 40.3% (52/129) and fatal TEAEs in 6.2% (8/129); all subjects were heavily pretreated and no fatal infections were considered related to epcoritamab.

Notably, the majority of FL subjects were enrolled and treated during the peak of the COVID-19 pandemic. COVID-19 infections had a significant impact, contributing to a considerable rise in the frequency of severe TEAEs of infections, as well as fatal TEAEs.

Important Potential Risks

Information 1: Risk of overdose due to medication errors

Risk-benefit impact: Potential events of overdose due to medication errors may occur with the administration of epcoritamab.

LBCL/DLBCL: A total of 3 medication errors occurred in the epcoritamab clinical program and were included in the Summary of Clinical Safety (SCS) (2 in Study GCT3013-01 and 1 in Study GCT3013-02 [originally ascribed to Study GCT3013-04]). An additional medication error occurred in Study GCT3013-05 after data lock and was also included in the SCS. Three medication errors resulted in accidental overdoses, 2 with a priming dose and 1 with a full dose of 24 mg. The patient who experienced a medication error in Study GCT3013-05 also experienced non-serious AEs of headache and chills on Study Day 2, which resolved without treatment.

FL: One medication error has been reported in FL subjects receiving epcoritamab monotherapy across the Primary Safety Analysis Set of Safety Pool 01 R/R FL and the Supportive Safety Analysis Set of Safety Pool 01+04 R/R FL as of the DLP. This medication error was an overdose (> 10% protocol-prescribed dose) in the priming dose during the escalation part of the -01 study; the intended epcoritamab dose was 0.08 mg, but the subject was administered a dose of 0.96 mg. The overdose was not associated with any adverse clinical outcome.

All Indications: Overall, there have been no reports of overdose due to medication errors for epcoritamab that directly caused life-threatening events or death. Based on current clinical trial evidence, the risk of overdose due to medication errors frequency is low and most reports were non-serious in severity with no adverse clinical outcomes reported. Healthcare professionals qualified in the use of anti-cancer therapies are aware of the potential for overdose with medicinal products and have the appropriate measures in place as part of routine clinical practice. Medication errors risk is monitored via routine pharmacovigilance.

Missing information

Information 1: Long-term safety

Risk-benefit impact: There are limited data available regarding safety with long-term use of epcoritamab for LBCL/DLBCL and FL populations.

Data to be Collected Post-Authorization:

LBCL/DLBCL: Ongoing studies in R/R DLBCL monotherapy (GCT3013-01 and GCT3013-05).

FL: ongoing studies in R/R FL (GCT3013-01 and M20-638).

SVII.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

Not Applicable.

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1 Presentation of Important Identified Risks and Important Potential Risks

Important Identified Risk 1: Cytokine Release Syndrome (CRS)

MedDRA terms: Preferred Term (PT) Cytokine release syndrome

Potential Mechanisms:

Activation of the T-cells upon binding to CD3 simultaneous with CD20 binding with release of granzymes and cytokines will induce lysis of the cells in close proximity (i.e., the CD20 expressing cell). Available clinical safety data from compounds and drugs engaging with T-cell as the mode of action draw attention to CRS as a frequent adverse event (AE). The pathophysiology of CRS is incompletely understood. Interleukin 6 (IL-6) seems to hold a key role in CRS pathophysiology since highly elevated IL-6 levels are seen in patients with CRS and in animal models (Shimabukuro-Vornhagen 2018).

Evidence Source(s) and Strength of Evidence:

Most frequent AE across epcoritamab clinical trials and literature (Salvaris 2021)

Characterization of the Risk:

LBCL/DLBCL:

	GCT3013-01 ESC+EXP		GCT3013-01 + GCT3013-04 ESC+EXP
	LBCL (N = 167)	DLBCL (N = 148)	All B-NHL (N = 374)
Subjects with at least 1 CRS event	84 (50.3%)	73 (49.3%)	230 (61.5%)
Grade 1	52 (31.1%)	45 (30.4%)	135 (36.1%)
Grade 2	28 (16.8%)	24 (16.2%)	79 (21.1%)
Grade 3	4 (2.4%)	4 (2.7%)	15 (4.0%)
Grade 4	0	0	1 (0.3%)

	LBCL (N = 167)	DLBCL (N = 148)	All B-NHL (N = 374)
Subjects treated with anti-cytokine therapy	25 (15.0%)	21 (14.2%)	81 (21.7%)
Tocilizumab	25 (15.0%)	21 (14.2%)	80 (21.4%)
Other	0	0	1 (0.3%)
Subjects with CRS leading to treatment discontinuation	1 (0.6%)	1 (0.7%)	2 (0.5%)
Median time to first CRS onset, days (min, max)	16.0 (1, 55)	16.0 (1, 31)	16.0 (1, 59)
Median time to CRS resolution, days (min, max)	3.0 (1, 27)	3.0 (1, 15)	3.0 (1, 36)

CRS Grading was based on ASTCT consensus criteria (Lee 2019).

Most CRS events occurred during the first cycle of treatment, with the highest incidence occurring after the first full dose administration of epcoritamab, which correlates with the overall median time to first CRS onset of 16 days. CRS events were generally grade 1 or 2. For LBCL, 4 subjects (2.4%) had grade 3 events and no grade 4 events. One subject with mantle cell lymphoma (MCL) in the All B-NHL group had grade 4 CRS. There were no grade 5 CRS events. Median time to CRS event resolution was 3.0 days.

FL:

	GCT3013-01 ESC+EXP (2-step SUD)	GCT3013-01 EXP (3-step SUD)
	FL (N = 129)	FL (N = 86)
Subjects with at least 1 CRS event	86 (66.7%)	42 (48.8%)
Grade 1	52 (40.3%)	34 (39.5%)
Grade 2	32 (24.8%)	8 (9.3%)
Grade 3	2 (1.6%)	0
Grade 4	0	0
Grade 5	0	0
Subjects treated with anti-cytokine therapy	31 (36.0%)	10 (23.8%)
Tocilizumab	31 (36.0%)	10 (23.8%)
Other	0	0
Subjects with CRS leading to treatment discontinuation	0	0

Median time to CRS resolution, days (min, max)	2.0 (1, 54)	2.0 (1,14)

CRS Grading was based on ASTCT consensus criteria (Lee 2019).

In Study GCT3013-01 for FL subjects receiving the 2-step SUD regimen, most CRS events occurred during the first cycle of treatment. The highest incidence of CRS occurred after the first full dose administration of epcoritamab. The median time to onset from the most recent dosing (at an event level) was 2.0 days. There was an overall incidence of CRS (Grade 1-3) at 66.7% (86/129), with the majority of these events generally Grade 1 or 2. Two (1.6%) subjects had Grade 3 CRS events, and no subjects had Grade 4 or 5 CRS events. The median time for resolution of CRS events was 2.0 days.

In the optimization part of study GCT3013-01 for FL subjects receiving the 3-step SUD regimen, most CRS events occurred during the first cycle of treatment. The median time to onset from the most recent dosing (at the event level) was 4.0 days. CRS events were Grade 1 or 2, and there were no reports of Grade 3 or higher of CRS. The median time to CRS resolution was 2.0 days.

Risk Factors and Risk Groups:

No risk factors and no risk groups have been identified in epcoritamab clinical trials. Risks identified in literature include but are not limited to: high disease burden, preexisting thrombocytopenia and endothelial activation, lymphodepleting therapy with fludarabine and cyclophosphamide, previous cardiovascular disease or organ dysfunction (Salvaris 2021, Schubert 2021, Xiao 2021). Children seem to be at a higher risk of developing CRS than adults (Shimabukuro-Vornhagen 2018).

Preventability:

Mitigation strategies include dose titration (including 2-step SUD regimen [a priming and an intermediate dose] in DLBCL or 3-step SUD regimen [a priming dose, first intermediate dose, and second intermediate dose] in FL), with adequate hydration and prophylactic corticosteroids (dexamethasone preferable), and close monitoring. Patients should be monitored for signs and symptoms of CRS following epcoritamab administration as described in the product label. At the first signs of symptoms of CRS, treatment of supportive care with tocilizumab and/or corticosteroids should be instituted as indicated in the product label. Patients should be advised to contact their healthcare professional and seek immediate medical attention should signs or symptoms associated with CRS occur at any time. Management of CRS may require either temporary delay or discontinuation of epcoritamab based on the severity of CRS.

Detailed information and guidance to mitigate the risk (including dose titration, prophylaxis, and monitoring measures) are provided in the product label and additional risk minimization measure (Patient Card) targeted to patients.

Impact on the Risk-Benefit Balance of the Product:

CRS is generally manageable with appropriate preventative measures and guidance on management, as well as subject monitoring, dose delays, and/or supportive care. Failure to respond to supportive care could lead to serious life-threatening or fatal CRS events.

Public Health Impact:

As oncologists are experienced in identifying and treating CRS, the public health impact is considered to be low.

Important Identified Risk 2: Immune effector cell associated neurotoxicity syndrome (ICANS)

MedDRA terms: PT Immune effector cell associated neurotoxicity syndrome

Potential Mechanisms:

The exact mechanism is unknown. One proposed mechanism is the release of neurotoxic cytokines and chemokines by activated T cells en route to the CNS, causing inflammation at the neuroendothelium (Salvaris 2021, Stein 2019). Clinical data from compounds targeting CD19 and CD3, or CAR T-cells targeting CD19 report neurotoxicity (ICANS) as a frequent AE. Whether this is related to CD19, to CD3 or both as targets is unknown.

Evidence Source(s) and Strength of Evidence:

Epcoritamab clinical trials and literature (Salvaris 2021)

Characterization of the Risk:

LBCL/DLBCL

	GCT3013-01 ESC+EXP		**GCT3013-01 + GCT3013-04 ESC+EXP**
	LBCL (N = 167)	**DLBCL (N = 148)**	**All B-NHL (N = 374)**
Subjects with at least one ICANS event	10 (6.0%)	9 (6.1%)	23 (6.1%)
Grade 1	7 (4.2%)	6 (4.1%)	16 (4.3%)
Grade 2	2 (1.2%)	2 (1.4%)	6 (1.6%)
Grade 3	0	0	0
Grade 4	0	0	0
Grade 5	1 (0.6%)	1 (0.7%)	1 (0.3%)
Subjects with ICANS leading to treatment discontinuation	1 (0.6%)	1 (0.7%)	1 (0.3%)
Median time to first ICANS onset, days (min, max)	16.5 (8, 141)	17.0 (8, 141)	16.0 (5, 141)
Median time to ICANS resolution, days (min, max)	5.0 (1, 9)	3.5 (1, 9)	2.0 (1, 9)

ICANS Grading was based on ASTCT consensus criteria (Lee 2019).

ICANS was reported in approximately 6% of subjects in any group. For LBCL, 6.0% (10/167) of subjects experienced ICANS (all of the events were considered treatment-related) with most of the events either grade 1 (4.2%; 7 subjects) or grade 2 (1.2%; 2 subjects) and no grade 3 or 4 events. One (0.6%) subject had a fatal ICANS event (grade 5). The median time to onset was 16.5 days from initiation of epcoritamab. The ICANS event resolved in 9 of 10 subjects, with a median time to resolution of 5 days. The onset of ICANS can be concurrent with CRS, following resolution of CRS or in the absence of CRS.

FL:

	GCT3013-01 ESC+EXP (2-step SUD)	GCT3013-01 EXP (3-step SUD)
	FL (N = 129)	**FL (N = 86)**
Subjects with at least one ICANS event	8 (6.2%)	0
Grade 1	5 (3.9%)	0
Grade 2	3 (2.3%)	0
Grade 3	0	0
Grade 4	0	0
Grade 5	0	0
Subjects with ICANS leading to treatment discontinuation	0	0
Median time to first ICANS onset, days (min, max)	21.5 (14, 66)	0
Median time to ICANS resolution, days (min, max)	2.0 (1, 8)	0

ICANS Grading was based on ASTCT consensus criteria (Lee 2019).

In Study GCT3013-01 for FL subjects receiving the 2-step SUD regimen, ICANS was reported in 6.2% of subjects, all events either grade 1 (3.9%; 5 subjects) or grade 2 (2.3%; 3 subjects) and no grade 3, 4, or 5 events. The median time to onset was 21.5 days from initiation of epcoritamab. The ICANS event resolved in all 8 subjects, with a median time to resolution of 2 days. The onset of ICANS can be concurrent with CRS, following resolution of CRS or in the absence of CRS.

In Study GCT3013-01 for FL subjects receiving the 3-step SUD regimen, there were no reports of ICANS for the optimization part.

Risk Factors and Risk Groups: No risk factors and no risk groups were identified in epcoritamab clinical trials. Risks identified in literature include but are not limited to: Early and severe CRS with high levels of inflammatory cytokines, high disease burden, preexisting thrombocytopenia and endothelial activation, lymphodepleting therapy with fludarabine and cyclophosphamide, preexisting neurologic comorbidities (Schubert 2021, Xiao 2021).
Preventability: Mitigation strategies include dose titration (including 2-step SUD regimen [a priming and an intermediate dose] in DLBCL or optimized 3-step SUD regimen [a priming dose, first intermediate dose, and second intermediate dose] in FL), with adequate hydration and prophylactic corticosteroids (dexamethasone preferable), and close monitoring. Patients should be monitored for signs and symptoms of ICANS following epcoritamab administration as described in the product label. At the first signs or symptoms of ICANS, treatment should be instituted as indicated in the product label. Patients should be counseled on the signs and symptoms of ICANS and that the onset of event may be delayed, and instructed to contact their healthcare professional and seek immediate medical attention if signs and symptoms occur at any time. Epcoritamab should be delayed or discontinued as recommended in the product label. Detailed information and guidance to mitigate the risk (including dose titration, prophylaxis, and monitoring measures) is provided in the product label and additional risk minimization measure (Patient Card) targeted to patients.
Impact on the Risk-Benefit Balance of the Product: ICANS is generally manageable with appropriate preventative measures and guidance on management, as well as subject monitoring, dose delays, and/or supportive care. Failure to respond to supportive care could lead to serious life-threatening or fatal ICANS events.
Public Health Impact: As oncologists are experienced in identifying and treating ICANS following available guidelines (Lee 2019), the public health impact is considered to be low.

Important Identified Risk 3: Serious Infections MedDRA terms: System Organ Class Infections and Infestations (serious events)
Potential Mechanisms: Epcoritamab can cause immunomodulation of B- and T-cell interactions, B-cell depletion and subsequently hypogammaglobulinemia. Additionally, cytopenias observed during epcoritamab treatment may cause an increased risk of serious infections.
Evidence Source(s) and Strength of Evidence: Epcoritamab clinical trials and literature (Longhitano 2021, Salvaris 2021)

Characterization of the Risk:

Patients with NHL have an increased risk of infection due to the underlying disease severity, and the risk varies based on the extent of disease, presence of cytopenias, use of cytotoxic agents, hematopoietic cell transplantation, and/or prophylactic anti-infectives. Aggressive NHL may result in T-cell defects, impacting both innate and cellular immunity. Patients with indolent B-cell non-Hodgkin lymphomas (B-NHLs) have an increased risk of infections which is caused by pathomechanisms of the diseases itself but also as a result of anti-tumor therapy (Lutz 2023)

Bispecific antibodies have been associated with the development of cytopenias, and neutropenia and lymphopenia are established risk factors for infection. Bispecific antibodies may also be associated with reduced levels of immunoglobulins, specifically hypogammaglobulinemia has been associated with an increased risk of infection (Longhitano 2021).

LBCL/DLBCL

TEAEs in System Organ Class Infections and Infestations	**GCT3013-01 ESC+EXP**		**GCT3013-01 + GCT3013-04 ESC+EXP**
	LBCL (N = 167)	**DLBCL (N = 148)**	**All B-NHL (N = 374)**
Subjects with at least 1 serious TEAE	27 (16.2%)	24 (16.2%)	70 (18.7%)
Serious TEAE by worst toxicity grade			
Grade 1	1 (0.6%)	1 (0.7%)	1 (0.3%)
Grade 2	3 (1.8%)	3 (2.0%)	8 (2.1%)
Grade 3	17 (10.2%)	14 (9.5%)	49 (13.1%)
Grade 4	2 (1.2%)	2 (1.4%)	3 (0.8%)
Grade 5	4 (2.4%)	4 (2.7%)	9 (2.4%)

For LBCL, serious TEAEs of infection were reported in 16.2% and fatal TEAEs in 2.4% of subjects; none of the fatal TEAEs were assessed as related to epcoritamab. The most frequently reported serious TEAEs of infection (reported for 2 or more subjects) included pneumonia in 2.4%, sepsis in 2.4%, COVID-19 in 1.8%, COVID-19 pneumonia in 1.8%, and cellulitis in 1.8% of subjects and 2 subjects (1.2%) each with bacteremia, septic shock, and upper respiratory tract infection. Fatal TEAEs of infection included COVID-19 in 1.2%, COVID-19 pneumonia in 0.6% and progressive multifocal leukoencephalopathy in 0.6% of subjects.

FL:

TEAEs in System Organ Class Infections and Infestations	GCT3013-01 ESC+EXP (2-step SUD)
	FL (N = 129)
Subjects with at least 1 serious TEAE	52 (40.3%)
Grade 1	0
Grade 2	5 (3.9%)
Grade 3	39 (30.2%)
Grade 4	0
Grade 5	8 (6.2%)

In Study GCT3013-01 for FL subjects receiving the 2-step SUD regimen, serious TEAEs of infection were reported in 40.3% and fatal TEAEs in 6.2% of subjects; none of the fatal TEAEs were assessed as related to epcoritamab. The most frequently reported serious TEAEs of infection by PT (reported for 2 or more subjects) included COVID-19 in 11.6%, COVID-19 pneumonia in 7.8%, Pneumonia in 5.4%, Pneumocystis jirovecii pneumonia in 2.3%, and 1.6% subjects each with Pneumonia pseudomonal, Staphylococcal bacteraemia, and Urinary tract infection. Fatal TEAEs of infection included COVID-19 pneumonia in 3.9% subjects, and 0.8% each with COVID-19, pneumonia and Pseudomonal sepsis. Notably, the majority FL subjects were enrolled and treated during the peak of the COVID-19 pandemic. As a result, serious COVID-19 infections were reported in FL subjects, including 11.6% with COVID-19 and 7.8% with COVID-19 pneumonia. Among these serious COVID-19 infections, fatal outcomes were reported for COVID-19 pneumonia in 3.9% and COVID-19 in 0.8%. Consequently, these COVID-19 infections had a significant impact, contributing to a considerable rise in the frequency of severe TEAEs of infections, as well as fatal TEAEs.

Risk Factors and Risk Groups:

No risk factors and no risk groups were identified in epcoritamab clinical trials. The epidemiology and risks for infections amongst patients managed with bispecific antibodies remain unclear (Longhitano 2021).

Infections are more common in patients with advanced stage of disease, prolonged leukopenia, low granulocyte count, lymphopenia, hypogammaglobulinemia, defective monocytes, reduced serum complement levels, longer length of disease, steroid use, bone marrow transplant recipients, and renal dysfunction.

Patients with CRS are at a high risk of infection and the immunosuppressive treatment that is administered for the treatment of CRS can mask some of the signs of infection thereby delaying diagnosis and treatment of infections. The mechanism that is responsible for the increased incidence of infection in patients with CRS is unknown (Longhitano 2021, Shimabukuro-Vornhagen 2018).

Preventability: Administration of epcoritamab should be avoided in patients with clinically significant active systemic infections. As appropriate, prophylactic antimicrobials should be administered prior to and during treatment with epcoritamab. Patients should be monitored for signs and symptoms of infections before and after epcoritamab administration, and treated appropriately. In the event of febrile neutropenia, patient should be evaluated for infection and managed with antibiotics, fluids, and other supportive care, according to local guidelines. Detailed information and guidance to mitigate the risk (including prophylaxis and monitoring measures) is provided in the product label.
Impact on the Risk-Benefit Balance of the Product: Infections are generally manageable following standard guidelines for supportive care. Failure to respond to supportive care could lead to serious life-threatening or fatal infections.
Public Health Impact: As oncologists are experienced in identifying and treating infections, the public health impact is considered to be low.

Important Potential Risk 1: Risk of overdose due to medication errors

MedDRA terms: SMQ Medication Errors (Broad)

Potential Mechanisms:

The product must be diluted prior to administration of the 0.16 mg priming and 0.8 mg intermediate doses and re-priming may be necessary following delays in therapy. Potential medication errors leading to overdose could occur in the prescribing, preparation, dispensing, and administration of epcoritamab.

Evidence Source(s) and Strength of Evidence:

Epcoritamab clinical trials

Characterization of the Risk:

Potential events of overdose due to medication errors may occur with the administration of epcoritamab.

LBCL/DLBCL: A total of 3 medication errors occurred in the epcoritamab clinical program and were included in the SCS (2 in Study GCT3013-01 and 1 in Study GCT3013-02 [originally ascribed to Study GCT3013-04]). An additional medication error occurred in Study GCT3013-05 after data lock and was also included in the SCS. Three medication errors resulted in accidental overdoses, 2 with a priming dose and 1 with a full dose of 24 mg. The patient who experienced a medication error in Study GCT3013-05 also experienced non-serious AEs of headache and chills on Study Day 2, which resolved without treatment.

FL: One medication error has been reported in FL subjects receiving epcoritamab monotherapy across the Primary Safety Analysis Set of Safety Pool 01 R/R FL and the Supportive Safety Analysis Set of Safety Pool 01+04 R/R FL as of the DLP. This medication error was an overdose (> 10% protocol-prescribed dose) in the priming dose during the escalation part of the -01 study; the intended epcoritamab dose was 0.08 mg, but the subject was administered a dose of 0.96 mg. The overdose was not associated with any adverse clinical outcome.

All Indications: Overall, there have been no reports of overdose due to medication error for epcoritamab that directly caused life-threatening events or death. Based on current clinical trial evidence, the risk of overdose due to medication errors frequency is low and most reports were non-serious in severity with no adverse clinical outcomes reported. Healthcare professionals qualified in the use of anti-cancer therapies are aware of the potential for overdose with medicinal products and have the appropriate measures in place as part of routine clinical practice. Medication errors risk is monitored via routine pharmacovigilance.

Risk Factors and Risk Groups:

No risk factors and no risk groups were identified in epcoritamab clinical trials.

Preventability:

To mitigate the risk of overdose due to medication errors with epcoritamab, comprehensive instructions for dosing schedule, dilution, preparation, and administration procedures are provided in the product labeling.

Impact on the Risk-Benefit Balance of the Product:

The causes for these overdoses due to medication errors are not related to the product quality and usually can be avoided if the approved prescribing instruction for dilution, preparation, and administration is strictly followed. The benefit-risk balance remains positive.

Public Health Impact: As none of the AEs reported in the overdoses due to medication error cases were life-threatening or fatal, the public health impact is considered to be low.

SVII.3.2 Presentation of the Missing Information

Missing information 1: Long-term safety
Evidence source: Limited data are available on long-term exposure. The long-term safety of epcoritamab will be monitored through ongoing clinical studies: R/R LBCL/DLBCL monotherapy - GCT3013-01 and GCT3013-05 R/R FL - GCT3013-01 and M20-638

Module SVIII Summary of the Safety Concerns

Table 8. Summary of Safety Concerns

Summary of Safety Concerns for All Indications	
Important identified risks	CRS ICANS Serious infections
Important potential risks	Risk of overdose due to medication errors
Missing information	Long-term safety

Part III: Pharmacovigilance Plan (Including Post-Authorization Safety Studies)

III.1 Routine Pharmacovigilance Activities

No routine activities beyond adverse reactions reporting and signal detection are planned for the product.

III.2 Additional Pharmacovigilance Activities

Additional PV activities addressing safety concerns include:

LBCL/DLBCL

- Evaluation of safety in long-term exposure (Study GCT3013-01)
- Evaluation of long-term safety with comparator data (Study GCT3013-05)

FL

- Evaluation of safety in long-term exposure (Studies GCT3013-01 and M20-638)
- Evaluation of long-term safety with comparator data (Study M20-638)
- CRS, ICANS, and serious infections (Study M20-638)

GCT3013-01 Summary

Study Short Name and Title:

A Phase 1/2, Open-Label, Dose-Escalation Trial of GEN3013 in Patients with R/R or Progressive mature BCL

Rationale and Study Objectives:

The purpose of the dose escalation part of this trial is to establish the maximum tolerated dose (MTD) of epcoritamab and the recommended Phase 2 dose (RP2D) of epcoritamab in patients with R/R or progressive BCL.

The purpose of the expansion part of this trial is to evaluate the efficacy and safety of epcoritamab at the RP2D in patients with the following B-cell non-Hodgkin lymphoma (B-NHL) with limited therapeutic options:

- Aggressive R/R B-NHL (aNHL cohort) including:
  - DLBCL
  - HGBCL
  - PMBCL
  - FL grade 3b
- Indolent R/R B-NHL (iNHL cohort) including:
  - FL grade 1 to 3a
  - Marginal zone lymphoma (MZL)
  - SLL
- MCL

The purpose of the separate optimization part is to explore alternative strategies to reduce the incidence and severity of CRS. Three cohorts (i.e., subjects with DLBCL, FL Grades 1-3A, and MCL) will investigate alternative doses with the goal of further lowering the rate of ≥ Grade 2 CRS events.

Dose escalation (Phase 1):

- Primary Objective

- Determine MTD and RP2D of epcoritamab monotherapy

- Secondary Objectives
  - Establish tolerability of epcoritamab
  - Establish PK profile after single and multiple doses
  - Evaluate immunogenicity
  - Evaluate anti-lymphoma activity

Expansion (Phase 2):

- Primary Objective
  - Evaluate clinical efficacy as determined by Lugano criteria
- Secondary Objectives
  - To further evaluate clinical efficacy as determined by Lugano criteria
  - To evaluate the clinical efficacy as determined by LYmphoma Response to Immunomodulatory therapy Criteria (LYRIC)
  - To further evaluate clinical efficacy
  - To evaluate minimal residual disease (MRD) status as a clinical efficacy endpoint
  - To evaluate safety and tolerability of epcoritamab
  - To evaluate the PK and immunogenicity of epcoritamab
  - To evaluate patient-reported outcomes (PROs) related to lymphoma symptoms

Dose Optimization

- Primary Objective
  - Determine whether an alternative priming/intermediate dose regimen may reduce CRS risk
- Secondary Objective
  - To evaluate safety and tolerability of alternative priming/intermediate dosing regimens
  - Establish PK and pharmacodynamic profile after single and multiple doses
  - Evaluate immunogenicity
  - Evaluate clinical efficacy as determined by Lugano criteria
  - To evaluate MRD status as a clinical efficacy endpoint

Study Design:

This is an open label, Phase 1/2 trial in patients with R/R or progressive mature BCL. The dose escalation part will determine the MTD and RP2D. The expansion part will be conducted in 2 stages. In stage 1, patients with DLBCL, FL Grade 1 to 3a, and R/R MCL will be enrolled, and response data will be collected. Following an interim futility analysis, additional patients with DLBCL, FL Grade 1 to 3a, and R/R MCL may be enrolled for stage 2 in order to reach the sample size required for statistical analysis. In addition, patients with other aNHL or iNHL subtypes as described above may be enrolled in stage 2. A separate optimization part will explore alternative priming/intermediate dose levels to reduce the incidence and severity of CRS in patients with DLBCL, FL Grades 1-3A, and MCL.

Study Population:

The dose escalation part of the trial will include up to 70 patients with R/R and/or progressive mature BCL. The expansion part of the trial will include up to 416 patients with specified aNHLs, iNHLs, or MCL. Approximately up to 120 subjects with DLBCL will be enrolled into the optimization part. If a potentially more optimal priming and intermediate dose regimen is identified during the optimization part, additional DLBCL subjects may be included. Additionally, approximately up to 100 and 80 subjects, respectively, with FL Grades 1-3A and MCL may be enrolled into the optimization part.

Milestones:

Study is ongoing. Final clinical study report (CSR) planned for Quarter 4 of 2030.

GCT3013-05 Summary

Study Short Name and Title:

A Randomized, Open-Label, Phase 3 Trial of Epcoritamab versus (vs) Investigator's Choice (IC) Chemotherapy in R/R DLBCL

Rationale and Study Objectives:

The primary objective of this trial is to evaluate the efficacy of epcoritamab compared to IC of chemotherapy in subjects with R/R DLBCL, who have failed or are ineligible for HDT-ASCT.

- Primary Objective
  - Compare the clinical efficacy of epcoritamab to SOC (rituximab, gemcitabine, and oxaliplatin [R-GemOx] or BR)
- Secondary Objectives
  - Compare other measures of epcoritamab efficacy to SOC
  - Compare safety and tolerability of epcoritamab to SOC
  - Evaluate immunogenicity

- To compare PROs related to lymphoma symptoms between epcoritamab and SOC

Study Design:

This is an open-label, randomized (1:1), global, Phase 3 trial of epcoritamab vs prespecified IC of chemotherapy in subjects with R/R DLBCL who failed or are ineligible for ASCT. Eligible subjects will be randomized to either epcoritamab or IC of R-GemOx or BR; prior to randomization, the investigator must select and document reason for the intended choice of chemotherapy (which the subject will receive if randomized to the investigator choice); no change in chemotherapy is permitted for an individual subject during the active treatment phase of the trial. Randomization will be stratified by number of prior lines of therapy (1 vs > 1), Eastern Cooperative Oncology Group Performance Status (0 to 1 vs 2), prior ASCT (yes vs no), and prior CAR T cell therapy (yes vs no).

Approximately 480 subjects (240 in each arm) will be enrolled in the trial with a primary endpoint of OS. An interim analysis will occur after approximately 180 deaths have occurred overall. An independent data monitoring committee (IDMC) will assess safety and efficacy data during the trial, according to the IDMC Charter.

Study Population:

Approximately 480 subjects aged 18 years or older with R/R DLBCL who failed a previous ASCT or are ineligible for ASCT at screening will be enrolled. The number of subjects with only 1 prior therapy will be capped at approximately 120 subjects (approximately 25% of total enrollment).

Milestones:

Study is ongoing. Primary analysis CSR planned for Quarter 2 of 2026 and final CSR planned for Quarter 1 of 2029.

Planned safety data to be included in the final CSR:

- Incidence of the following AEs: CRS, serious infections, and ICANS, and other AEs such as: injection site reactions, neutropenia/cytopenia, neurological events, CTLS, and tumor flares.
- Comparative safety data analysis
- Safety analysis for patients with prior CAR-T

M20-638 Summary

Study Short Name and Title:

A Phase 3, Open-Label Study to Evaluate Safety and Efficacy of Epcoritamab in Combination with rituximab and lenalidomide (R^2) compared to R^2 in Subjects with R/R FL

Rationale and Study Objectives:

- Primary Objective
  - To evaluate the efficacy, safety, and tolerability of epcoritamab 48 mg in combination with R^2 compared to R^2 alone in subjects with R/R FL
- Secondary Objectives
  - To evaluate whether epcoritamab 48 mg in combination with R^2 compared to R^2 alone can improve clinical outcomes as measured by key secondary endpoints (including CR, overall survival [OS], and MRD negativity) in subjects with R/R FL

Study Design:

This is an open-label, randomized, global, Phase 3 trial evaluating the safety and efficacy of epcoritamab in combination with (rituximab and lenalidomide) R^2 compared to R^2 in subjects with R/R FL after at least one prior anti-lymphoma regimen that contained an antiCD20 monoclonal antibody in combination with chemotherapy. Eligible subjects will be randomized to epcoritamab 48 mg in combination with R^2, or R^2 alone.

Randomization will be stratified by the following:

- Disease Status/History:
  - Subjects in 2L treatment: progression of disease ≤ 2 years from the date of initiation of frontline therapy (POD24)
  - Subjects in 2L treatment: progression of disease > 2 years from the date of initiation of frontline therapy
  - Subjects in 3L+ treatment: < 6 months since end of last therapy until randomization date
  - Subjects in 3L+ treatment: ≥ 6 months since end of last therapy until randomization date
- Region
  - United States (US)/Western Europe
  - Rest of world

Approximately 500 subjects will be enrolled in the study. From this, approximately 428 subjects will be included in the Intent to Treat (ITT) population in Arm A and Arm C. The PFS final analysis will occur after 171 PFS events have accumulated in the ITT population. After PFS final analysis, subjects will continue to be followed for OS. The OS final analysis will occur after approximately 135 OS events have accumulated in the ITT population. An IDMC will assess safety and efficacy data during the trial, according to the IDMC Charter.

Study Population:

Approximately 500 subjects aged 18 years or older with R/R FL after at least one prior anti-lymphoma regimen that contained an antiCD20 monoclonal antibody in combination with chemotherapy will be enrolled.

Milestones:

Study is ongoing. Final CSR planned for Quarter 4 of 2030.

III.3 Summary Table of Additional Pharmacovigilance Activities

Table 9. Ongoing and Planned Additional Pharmacovigilance Activities

Study/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 1 - Imposed mandatory additional PV activities which are conditions of the marketing authorization				
Not Applicable				
Category 2 - Imposed mandatory additional PV activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
GCT3013-01: A Phase 1/2, OL, Dose-Escalation Trial of GEN3013 in Patients with R/R or Progressive BCL Ongoing	Evaluate the safety and efficacy of epcoritamab monotherapy	Long-term safety (maximum 5 years after last patient's first dose, treated until disease progression unless meet treatment discontinuation criteria)	Final CSR	Planned for Quarter 4 of 2030

Study/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
GCT3013-05: Randomized, OL, Ph3 Trial of Epcoritamab vs IC Chemotherapy in R/R DLBCL Ongoing	Evaluate safety and efficacy of epcoritamab compared to SOC (R-GemOx or BR)	Long-term safety with comparator data (maximum 5 years after last patient randomized) CRS, ICANS, and serious infections.	Primary analysis CSR Final CSR	Planned for Quarter 2 of 2026 Planned for Quarter 1 of 2029
M20-638: A Ph3, OL Trial of Epcoritamab in Combination with R^2 compared to R^2 in R/R FL Ongoing	Evaluate the safety and efficacy of epcoritamab in combination with R^2 compared to R^2 alone	Long-term safety (maximum 5 years after last patient's first dose, treated until disease progression unless meet treatment discontinuation criteria) Long-term safety with comparator data (maximum 5 years after last patient randomized) CRS, ICANS, and serious infections.	Final CSR	Planned for Quarter 4 of 2030
Category 3 - Required additional PV activities				
Not Applicable				

BCL = B-cell lymphoma; BR = bendamustine + rituximab; CRS = Cytokine Release Syndrome; CSR = clinical study report; DLBCL = diffuse large B-cell lymphoma; Gen3013 = epcoritamab; IC = Investigator's choice; ICANS = Immune Effector cell-associated neurotoxicity syndrome; OL = open-label; Ph = phase; PV = pharmacovigilance; R^2 = rituximab and lenalidomide; R-GemOx = rituximab + gemcitabine-oxaliplatin; R/R= relapsed/refractory; SOC = standard of care

Part IV: Plans for Post-Authorization Efficacy Studies

Not Applicable

Part V: Risk Minimization Measures (Including Evaluation of the Effectiveness of Risk Minimization Activities)

Risk Minimization Plan

V.1 Routine Risk Minimization Measures

Table 10. Description of Routine Risk Minimization Measures by Safety Concern

Safety Concern	Routine Risk Minimization Activities
CRS	Routine risk communication: • SmPC Section 4.2 - Posology and method of administration includes Recommended Dose Modifications for CRS • SmPC Section 4.4 - Special warnings and precautions for use • SmPC Section 4.8 - Undesirable effects Routine risk minimization activities recommending specific clinical measures to address the risk: • SmPC Section 4.2 - Posology and method of administration includes CRS Grading and Management Guidance Other routine risk minimization measures beyond the Product Information: • Prescription-only medicine
ICANS	Routine risk communication: • SmPC Section 4.2 - Posology and method of administration includes Recommended Dose Modifications for ICANS • SmPC Section 4.4 - Special warnings and precautions for use • SmPC Section 4.8 - Undesirable effects Routine risk minimization activities recommending specific clinical measures to address the risk: • SmPC Section 4.2 - Posology and method of administration includes ICANS Grading and Management Guidance Other routine risk minimization measures beyond the Product Information: • Prescription-only medicine

Safety Concern	Routine Risk Minimization Activities
Serious Infections	Routine risk communication: • SmPC Section 4.4 - Special warnings and precautions for use • SmPC Section 4.8 - Undesirable effects Routine risk minimization activities recommending specific clinical measures to address the risk: • None Other routine risk minimization measures beyond the Product Information: • Prescription-only medicine
Risk of overdose due to medication errors	Routine risk communication: • SmPC Section 4.2 - Posology and method of administration • SmPC Section 4.9 – Overdose • SmPC Section 6.6 – Special precautions for disposal and other handling Routine risk minimization activities recommending specific clinical measures to address the risk: • None Other routine risk minimization measures beyond the Product Information: • Prescription-only medicine
Long-term safety	Routine risk communication: • None Routine risk minimization activities recommending specific clinical measures to address the risk: • None Other routine risk minimization measures beyond the Product Information: • Prescription-only medicine

V.2 Additional Risk Minimization Measures

Additional Risk Minimization 1:

Patient Card

A Patient Card targeted to patients treated with epcoritamab will be implemented to minimize the important identified risks of CRS and ICANS.

Objectives:

- The objective of the Patient Card is to minimize the risk of CRS and ICANS by:
  - Increasing patient awareness of CRS and ICANS
  - Providing information on signs and symptoms of CRS and ICANS

- Alerting patients to promptly contact their HCPs/emergency care if they observe any of the signs or symptoms of CRS and ICANS
- Alerting HCPs treating the patient at any time, including in conditions of emergency, that the patient is using epcoritamab.

Rationale for the Additional Risk Minimization Activity:

A Patient Card is considered necessary to communicate to patients the risk of CRS and ICANS and to describe CRS and ICANS signs and symptoms to prompt patient actions to seek immediate medical attention in case of their occurrence. The Patient Card will also include information for any HCP providing care (including emergency) so the patient can be evaluated and treated for CRS and ICANS in a timely manner.

Target Audience and Planned Distribution Path:

Target audience includes all patients using epcoritamab. The Patient Card will be available in print or electronically. The Patient Card will be disseminated to HCPs who would then distribute the Patient Card to patients who are prescribed epcoritamab. Depending on local regulations or competent authority guidance, additional methods of distribution may also be applied to ensure all patients will receive the Patient Card in a timely manner. HCPs will be provided information on how to request additional Patient Cards.

Plans to Evaluate the Effectiveness of the Interventions and Criteria for Success:

None.

V.3 Summary of Risk Minimization Measures and Pharmacovigilance Activities

Table 11. Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
CRS	Routine risk minimization measures: • SmPC Section 4.2 - Posology and method of administration includes Recommended Dose Modifications for CRS and CRS Grading and Management Guidance • SmPC Section 4.4 - Special warnings and precautions for use	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional PV activities: Study GCT3013-05 Study M20-638

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	• SmPC Section 4.8 - Undesirable effects Other routine risk minimization measures: • Prescription-only medicine Additional risk minimization measure: • Patient Card	
ICANS	Routine risk minimization measures: • SmPC Section 4.2 - Posology and method of administration includes Recommended Dose Modifications for ICANS and ICANS Grading and Management Guidance. • SmPC Section 4.4 - Special warnings and precautions for use • SmPC Section 4.8 - Undesirable effects Other routine risk minimization measures: • Prescription-only medicine Additional risk minimization measure: • Patient Card	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional PV activities: Study GCT3013-05 Study M20-638
Serious Infections	Routine risk minimization measures: • SmPC Section 4.4 - Special warnings and precautions for use • SmPC Section 4.8 - Undesirable effects Other routine risk minimization measures: • Prescription-only medicine	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional PV activities: Study GCT3013-05 Study M20-638
Risk of overdose due to medication errors	Routine risk minimization measures: • SmPC Section 4.2 - Posology and method of administration • SmPC Section 4.9 – Overdose • SmPC Section 6.6 – Special precautions for disposal and other handling Other routine risk minimization measures: • Prescription-only medicine	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional PV activities: None

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Long-term safety	Routine risk minimization measures: • None Other routine risk minimization measures: • Prescription-only medicine	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional PV activities: Study GCT3013-01 Study GCT3013-05 Study M20-638

Part VI: Summary of the Risk Management Plan

Summary of Risk Management Plan for Epcoritamab

This is a summary of the risk management plan (RMP) for epcoritamab. The RMP details important risks of epcoritamab, how these risks can be minimized, and how more information will be obtained about epcoritamab risks and uncertainties (missing information).

Epcoritamab's summary of product characteristics (SmPC) and its package leaflet give essential information to health care professionals (HCPs) and patients on how epcoritamab should be used.

This summary of the RMP for epcoritamab should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all of which are part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of epcoritamab's RMP.

I The Medicine and What it Is Used For

Epcoritamab as monotherapy is indicated for the treatment of:

- Adult patients with relapsed or refractory (R/R) diffuse large B-cell lymphoma (DLBCL) after 2 or more lines of systemic therapy
- Adult patients with R/R follicular lymphoma (FL) after 2 or more lines of systemic therapy.

See SmPC for the full indication statements. It contains epcoritamab as the active substance and it is given by subcutaneous injection.

Further information about the evaluation of epcoritamab's benefits can be found in Epcoritamab's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage.

II Risks Associated with the Medicine and Activities to Minimize or Further Characterize the Risks

Important risks of epcoritamab, together with measures to minimize such risks and the proposed studies for learning more about epcoritamab risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and HCPs;
- Important advice on the medicine's packaging;
- The authorized pack size – the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status – the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimize its risks.

Together, these measures constitute **routine risk minimization** measures.

In the case of epcoritamab, these measures are supplemented **with additional risk minimization measures** mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute **routine pharmacovigilance activities**.

If important information that may affect the safe use of epcoritamab is not yet available, it is listed under "missing information" below.

II.A List of Important Risks and Missing Information

Important risks of epcoritamab are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of epcoritamab. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

List of Important Risks and Missing Information	
Important identified risks	CRS
	ICANS
	Serious Infections
Important potential risks	Risk of overdose due to medication errors
Missing information	Long-term safety

II.B Summary of Important Risks

Important identified risk: CRS	
Evidence for linking the risk to the medicine	Most frequent AE across epcoritamab clinical trials and literature (Salvaris 2021).
Risk factors and risk groups	No risk factors and no risk groups were identified in epcoritamab trials. Risks identified in literature include but not limited to: High disease burden, preexisting thrombocytopenia and endothelial activation, lymphodepleting therapy with fludarabine and cyclophosphamide, previous cardiovascular disease or organ dysfunction (Schubert 2021, Xiao 2021). Children seem to be at a higher risk of developing CRS than adults (Shimabukuro-Vornhagen 2018).
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.2 - Posology and method of administration includes Recommended Dose Modifications for CRS and CRS Grading and Management Guidance • SmPC Section 4.4 - Special warnings and precautions for use • SmPC Section 4.8 - Undesirable effects • Prescription-only medicine Additional risk minimization measure: • Patient Card
Additional PV activities	Additional PV activities: • Study GCT3013-05 • Study M20-638 See Section II.C of this summary for an overview of the post-authorization development plan.

Important identified risk: ICANS	
Evidence for linking the risk to the medicine	Epcoritamab clinical trials and literature (Salvaris 2021)
Risk factors and risk groups	No risk factors and no risk groups were identified in epcoritamab trials. Risks identified in literature include but not limited to: Early and severe CRS with high levels of inflammatory cytokines, high disease burden, preexisting thrombocytopenia and endothelial activation, lymphodepleting therapy with fludarabine and cyclophosphamide, preexisting neurologic comorbidities (Schubert 2021, Xiao 2021).
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.2 - Posology and method of administration includes Recommended Dose Modifications for ICANS and ICANS Grading and Management Guidance • SmPC Section 4.4 - Special warnings and precautions for use • SmPC Section 4.8 - Undesirable effects • Prescription-only medicine Additional risk minimization measure: • Patient Card
Additional PV activities	Additional PV activities: • Study GCT3013-05 • Study M20-638 See Section II.C of this summary for an overview of the post-authorization development plan.

Important identified risk: Serious Infections	
Evidence for linking the risk to the medicine	Epcoritamab clinical trials and literature (Longhitano 2021, Salvaris 2021)
Risk factors and risk groups	No risk factors and no risk groups were identified in epcoritamab trials. The epidemiology and risks for infections amongst patients managed with bispecific antibodies remain unclear (Longhitano 2021). Infections are more common in patients with advanced stage of disease, prolonged leukopenia, hypogammaglobulinemia, low granulocyte count, defective monocytes, reduced serum complement levels, longer length of disease, steroid use, bone marrow transplant recipients, and renal dysfunction. Patients with CRS are at a high risk of infection and the immunosuppressive treatment that is administered for the treatment of CRS can mask some of the signs of infection thereby delaying diagnosis and treatment of infections. The mechanism that is responsible for the increased incidence of infection in patients with CRS is unknown (Longhitano 2021, Shimabukuro-Vornhagen 2018).
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.4 - Special warnings and precautions for use • SmPC Section 4.8 - Undesirable effects • Prescription-only medicine
Additional PV activities	Additional PV activities: • Study GCT3013-05 • Study M20-638 See Section II.C of this summary for an overview of the post-authorization development plan.

Important potential risk: Risk of overdose due to medication errors	
Evidence for linking the risk to the medicine	Epcoritamab clinical trials
Risk factors and risk groups	No risk factors and no risk groups were identified in epcoritamab clinical trials.
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.2 - Posology and method of administration • SmPC Section 4.9 – Overdose • SmPC Section 6.6 – Special precautions for disposal and other handling • Prescription-only medicine

Missing information: Long-term safety	
Risk minimization measures	Routine risk minimization measures: • Prescription-only medicine
Additional PV activities	Additional PV activities: • Study GCT3013-01 • Study GCT3013-05 • Study M20-638 See Section II.C of this summary for an overview of the post-authorization development plan.

II.C Post-Authorization Development Plan

II.C.1 Studies Which are Conditions of the Marketing Authorization

The following studies are conditions of the marketing authorization:

GCT3013-01 summary

Purpose of the study:

The purpose of the dose escalation part of this trial is to establish the MTD of epcoritamab and the RP2D of epcoritamab in patients with R/R or progressive BCL.

The purpose of the expansion part of this trial is to evaluate the efficacy and safety of epcoritamab at the RP2D in patients with the following B-NHL with limited therapeutic options:

- Aggressive R/R B-NHL (aNHL cohort) including:
  - DLBCL
  - HGBCL
  - PMBCL
  - FL grade 3b
- Indolent R/R B-NHL (iNHL cohort) including:
  - FL grade 1 to 3a
  - MZL
  - SLL
- MCL

The purpose of the separate optimization part is to explore alternative strategies to reduce the incidence and severity of CRS. Three cohorts (i.e., subjects with DLBCL, FL Grades 1-3A, and MCL) will investigate alternative doses with the goal of further lowering the rate of ≥ Grade 2 CRS events.

GCT3013-05 Summary

Purpose of the study: The primary objective of this trial is to evaluate the efficacy of epcoritamab compared to IC of chemotherapy in subjects with R/R DLBCL, who have failed or are ineligible for HDT-ASCT.

M20-638 Summary

Purpose of the study: The primary objective of this trial is to evaluate the efficacy, safety, and tolerability of epcoritamab 48 mg in combination with R^2 compared to R^2 alone in subjects with R/R FL.

II.C.2 Other Studies in Post-Authorization Development Plan

None

Part VII: Annexes

Annex 4. Specific Adverse Drug Reaction Follow-Up Forms

Follow-up forms
Not Applicable

Annex 6. Details of Proposed Additional Risk Minimization Activities

Key messages of the additional risk minimization measure

Additional risk minimization measure to minimize the important identified risks of CRS and ICANS consist of a Patient Card targeted to patients treated with epcoritamab.

Prior to the launch of epcoritamab in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the patient card, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The MAH shall ensure that in each Member State where epcoritamab is marketed, HCPs who are expected to prescribe epcoritamab and patients treated with epcoritamab have access to/are provided with the Patient Card which will inform and explain to patients the risks of CRS and ICANS.

The Patient Card will contain the following key messages:

- Provide information on signs/symptoms of CRS and ICANS
- Alert patients to promptly contact their HCPs/emergency care if they observe any of the signs or symptoms of CRS and ICANS
- A warning message for HCPs treating the patient at any time, including in conditions of emergency, that the patient is using epcoritamab.
- Contact details of the epcoritamab prescriber