20 July 2023
EMA/CHMP/419797/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Tepkinly

International non-proprietary name: epcoritamab

Procedure No. EMEA/H/C/005985/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Table of contents

List of abbreviations

Abbreviation	Definition
AA	accelerated approval
ADA	anti-drug antibody (i.e., anti-epcoritamab antibody)
ADC	antibody-drug conjugate
ADCC	Antibody-dependent cellular cytotoxicity
ADCP	Antibody-dependent cellular phagocytosis
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
aNHL	aggressive B-cell non-Hodgkin lymphoma
aPTT	activated partial thromboplastin time
ASCT	autologous stem cell transplant
AST	alanine aminotransferase
ASTCT	American Society for Transplantation and Cellular Therapy
AUC	area under the concentration-time curve
AUC_{Cycle1}	area under the concentration-time curve over Cycle 1 (ie, Weeks 1 to 4)
BCL	B-cell lymphoma
BI	Biological intermediate
BLA	Biologics License Application
B-NHL	B-cell non-Hodgkin lymphoma
BR	bendamustine and rituximab
BSE	Bovine spongiform encephalopathy
bsAB	Bispecific antibody
C	cycle
C1D1	Cycle 1 Day 1
C1D8	Cycle 1 Day 8
C1D15	Cycle 1 Day 15
C1D22	Cycle 1 Day 22
C1q	Complement component 1q
CAR T	chimeric antigen receptor T-cell
CD	cluster of differentiation
CDC	Complement dependent cytotoxicity
CDR	Complementarity-determining region
CH1	Constant domain 1 of the heavy chain
CH2	Constant domain 2 of the heavy chain
CH3	Constant domain 3 of the heavy chain
CHO	Chinese hamster ovary
CHMP	Committee for Medicinal Products for Human Use
CHOP	cyclophosphamide, hydroxydaunorubicin, oncovin, and prednisone
CI	confidence interval
CLIPPERS	chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids
CLL	chronic lymphocytic leukemia
CMA	conditional marketing approval
C_{max}	maximum concentration
CO	clinical overview
COVID-19	coronavirus disease 2019
CPP	Critical process parameters
CQA	Critical quality attribute
CR	complete response
CrCl	creatinine clearance
CRS	cytokine release syndrome
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CTD	Common technical document
CTLS	clinical tumor lysis syndrome
Da	Dalton
DH	double-hit

Abbreviation	Definition
DLBCL	diffuse large B-cell lymphoma
DOCR	duration of complete response
DoE	Design of Experiment
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EQ-5D-3L	European Quality of Life 5 Dimensions 3 Level Version
ESMO	European Society for Medical Oncology
EU	European Union
Fab	Fragment, antigen binding
FACT-Lym	Functional Assessment of Cancer Therapy - Lymphoma
Fc	Fragment, crystallizable of heavy chain
FcγR	Fc-gamma receptor
FDA	Food and Drug Administration
FIH	first-in-human
FISH	fluorescence in situ hybridization
FL	follicular lymphoma
FU	Follow up
FL3B	follicular lymphoma grade 3B
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
Gem-Ox	gemcitabine and oxaliplatin
GM	Geometric mean
GMP	Good manufacturing practice
HC	Heavy chain
HCP	Host cell proteins
HCP	health care provider
HDT	high-dose therapy
HH	Heavy-heavy chain
HHL	Heavy-heavy-light chain
HL	Heavy-light chain
HGB(C)L	high-grade B-cell lymphoma
HMWS	High molecular weight species
ICANS	immune effector cell-associated neurotoxicity syndrome
ICE	immune effector cell-associated encephalopathy assessment tool
ICH	International Conference on Harmonization
Ig	Immunoglobulin
IGF-1	Insulin-like growth factor 1
IgG	Immunoglobulin G
IgG-1k	Immunoglobulin G 1, kappa type
IFN-γ	interferon-gamma
IgG1	immunoglobulin G1
IL	interleukin
iNHL	indolent B-cell non-Hodgkin lymphoma
INN	International nonproprietary names
INR	international normalized ratio
IPC	In-process control
IPI	international prognostic index
IRC	Independent Review Committee
ITT	intention-to-treat
LBCL	large B-cell lymphoma
LC	Light chain
LIVCA	Limit of in vitro cell age
LMWS	Low molecular weight species
LOT	lines of therapy
LYRIC	LYmphoma Response to Immunomodulatory therapy Criteria
mAb	monoclonal antibody
MCB	Master cell bank
MCL	mantle cell lymphoma
MDS	myelodysplastic syndrome
MoA	Mechanism of action
MRD	minimal residual disease
MTA	major therapeutic advantage

Abbreviation	Definition
MW	Molecular weight
MZL	marginal zone lymphoma
NCCN	National Comprehensive Cancer Network
NGH	Non-glycosylated heavy chain
NK	Natural killer
NHL	non-Hodgkin lymphoma
NOS	not otherwise specified
NR	not reached
NTI	narrow therapeutic index
ORR	overall response rate
OS	overall survival
PCP	*Pneumocystis jiroveci* pneumonia
PD	progressive disease
PFS	progression-free survival
Ph. Eur.	European Pharmacopoeia
PK	pharmacokinetic(s)
PMBC	peripheral mononuclear blood cell
PMBCL	primary mediastinal B-cell lymphoma
popPK	population pharmacokinetics
PR	partial response
PP	Process parameter
PPQ	Process performance qualification
PRS	Primary reference standard
PS80	Polysorbate 80
PRAC	Pharmacovigilance Risk Assessment Committee
PRO	patient-reported outcome
PT	preferred term
Q2W	once every 2 weeks
Q4W	once every 4 weeks
QSS	quasi-steady-state
QTcF	QT intervals corrected using Fridericia's formula
QW	once weekly
R-CHOP	rituximab plus cyclophosphamide, hydroxydaunorubicin, oncovin, and prednisone
RDI	relative dose intensity
RT	Room temperature
R-GemOx	rituximab, gemcitabine, and oxaliplatin
RP2D	recommended phase 2 dose
R/R	relapsed or refractory
RS	Richter’s syndrome
SAP	statistical analysis plan
SC	subcutaneous(ly)
SD	stable disease
SD	Standard deviation
SOC	system organ class
TEAE	treatment-emergent adverse event
TH	triple-hit
t_{max}	time to reach maximum concentration
TMDD	target-mediated drug disposition
TNF-α	tumor necrosis factor-alpha
TSE	Transmissible spongiform encephalopathy
TTCR	time to complete response
TTR	time to response
UF/DF	Ultrafiltration/diafiltration
ULN	upper limit of normal
US	United States
UTI	urinary tract infection
VAS	visual analog subscale
VH	Variable domain of the heavy chain
VL	Variable domain of the light chain
WCB	Working cell bank
WHO	World Health Organization
WRS	Working reference standard

1. Background information on the procedure

1.1. Submission of the dossier

The applicant AbbVie Deutschland GmbH & Co. KG submitted on 6 October 2022 an application for marketing authorisation to the European Medicines Agency (EMA) for Tepkinly, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 22 July 2021.

Tepkinly was designated as an orphan medicinal product EU/3/22/2581 on 24 February 2022 for the following indication: treatment of diffuse large B-cell lymphoma.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Tepkinly as an orphan medicinal product in the approved indication. More information on the COMP's review can be found in the orphan maintenance assessment report published under the 'Assessment history' tab on the Agency's website: www.ema.europa.eu/en/medicines/human/EPAR/Tepkinly.

The applicant applied for the following indication: Tepkinly is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8(3) of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

1.3. Information on paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0415/2022 on the agreement of a paediatric investigation plan (PIP).

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

1.5. Applicant's request(s) for consideration

1.5.1. Conditional marketing authorisation

The applicant requested consideration of its application for a Conditional marketing authorisation in accordance with Article 14-a of the above-mentioned Regulation.

1.5.2. New active substance status

The applicant requested the active substance epcoritamab contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.6. Protocol assistance

The applicant received the following Scientific Advice on the development relevant for the approved indication from the CHMP:

Date	**Reference**	**SAWP co-ordinators**
25/06/2020	EMEA/H/SA/4478/2/2020/III	Adriana Andric and Alexandre Moreau
15/10/2020	EMEA/H/SA/4478/3/2020/I	Karin Janssen van Doorn and Paolo Foggi

The Scientific Advice pertained to the following quality, non-clinical and clinical aspects:

- Comparability strategy for the manufacturing changes relating to transfer and scale-up as well as on the process performance qualification (PPQ) strategy to support the potential conditional MAA filing;
- Requirement for a 3-month repeat-dose toxicity study of epcoritamab in cynomolgus monkeys, and for a dedicated embryofetal developmental toxicity study,
- Unmet medical need exists in the proposed indication, R/R DLBCL;
- Design of the aNHL expansion cohort of the ongoing Phase 1/2 Trial GCT3013-01 to support a conditional marketing authorization (CMA), in particular the inclusion criteria, the primary and secondary endpoints, including MRD status, the statistical assumptions for the sample size calculation;
- Size of the safety database;
- Use of GCT3013-05 study of epcoritamab monotherapy versus investigator's choice (RGemOx or BR) as confirmatory trial under a specific obligation for a CMA;

1.7. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Johann Lodewijk Hillege Co-Rapporteur: Ingrid Wang

The application was received by the EMA on	6 October 2022
The procedure started on	27 October 2022
The CHMP Rapporteur's first Assessment Report was circulated to all	16 January 2023

CHMP and PRAC members on	
The CHMP Co-Rapporteur's assessment was circulated to all CHMP and PRAC members on	30 January 2023
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	30 January 2023
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	23 February 2023
The applicant submitted the responses to the CHMP consolidated List of Questions on	24 March 2023
The following GCP inspection(s) were requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:	
– A GCP inspection at 3 sites between 30 January and 17 March 2023. The outcome of the inspection carried out was issued on	09 May 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	2 May 2023
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	12 May 2023
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	25 May 2023
The applicant submitted the responses to the CHMP List of Outstanding Issues on	20 June 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	5 July 2023
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Tepkinly on	20 July 2023
The CHMP adopted a report on similarity of Tepkinly with Yescarta, Polivy, Minjuvi, Kymriah and Columvi on	20 July 2023
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product on	20 July 2023

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The claimed therapeutic indication is:

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

2.1.2. Epidemiology

Malignant lymphoma represents a disease entity characterized by malignant transformation of the cells from lymphoid tissue. Non–Hodgkin's lymphomas (NHL) are a heterogeneous group of lymphoproliferative disorders originating in B-lymphocytes, T-lymphocytes or natural killer cells. Approximately 80% are of B-cell origin (B-NHL) (Cheson et al., 2021). Clinically, NHL can be divided into aggressive NHL (aNHL; around 30%) and indolent NHL (iNHL). The applicant refers to aggressive B-NHL as large B-cell lymphoma (LBCL) in this submission, however formally this category also includes other subtypes besides LBCLs, such as Burkitt lymphoma and mantle cell lymphoma.

LBCL represents almost 30% of all cases of NHL. The most common histologic subtype is DLBCL NOS, which represents the majority (80%) of all cases of LBCL (Sehn and Salles, 2021). The annual incidence of DLBCL is estimated to be 5.6 per 100,000 in the US (SEER, 2022) and 7.4 per 100,000 in Europe (calculated from the proportion of DLBCL NOS in NHL [40.6%] from ECIS) (HMRN, 2020). Other LBCL entities are more rare and include primary mediastinal large B-cell lymphoma (PMBCL; around 6% of LBCL cases), high-grade B-cell lymphoma with double or triple hits (HBCL; 4–8% of LBCL cases), T-cell/histiocyte-rich large B-cell lymphoma (THRLBCL), EBV-positive diffuse large B-cell lymphoma, and more (Alaggio 2022, Swerdlow 2016). The incidence of PMBCL is 0.04 per 100,000 per year, respectively (Scott et al., 2018; SEER, 2022; Yu et al., 2021). In 2022 a new edition of the classification has been published, i.e. the 5th edition of the World Health Organization classification of the haematolymphoid neoplasms. In this edition, the entity of high-grade B-cell lymphoma with dual rearrangements of *MYC* and *BCL2* and/or *BCL6* has been renamed to high grade B-cell lymphoma with *MYC* and *BCL2* rearrangements. The classification of high-grade B-cell lymphoma NOS remains the same with the updated classification (Alaggio et al., 2022).

Follicular lymphoma (FL) comprises a group of malignant lymphomas consisting of follicle center cells. In the WHO classification, follicular lymphoma is a separate disease entity that is not included in the large B-cell lymphoma entity, but both fall under the category mature B-cell neoplasms (Sehn et al., 2021). Notably, the rare subtype FL grade 3B (FL3B) is traditionally treated as DLBCL due to similarities in biology (see below) and behaviour, and is often grouped as an aggressive NHL (aNHL).

The incidence of FL grade 3B is 0.26 per 100,000 per year, respectively (Scott et al., 2018; SEER, 2022; Yu et al., 2021). For (D)LBCL the median age at presentation is 64 years for patients and there is a male predominance with approximately 55 percent of cases occurring in men (Morton 2006). For PMBCL there is a female predominance and a median age at diagnosis in the third to fourth decade.

2.1.3. Biologic features

DLBCL not otherwise specified (DLBCL, NOS) represents the most common entity, and is defined by large-cell morphology as above, mature B-cell phenotype, and lack of criteria defining specific large B-cell lymphoma entities. Two main subtypes are recognized based on gene expression profile (GEP); the germinal centre B-cell-like (GCB) subtype and the activated B-cell-like (ABC) subtype. In total, 10 to 15% of the DLBCL cases are unclassifiable (Swerdlow 2016).

HGBCL is characterized by dual rearrangements of MYC and BCL2 and/or BCL6 (Swerdlow 2016). Note that this entity is renamed in the updated 5th WHO edition as described above to high grade B-cell lymphoma with *MYC* and *BCL2* rearrangements. The classification of high-grade B-cell lymphoma NOS remains the same with the updated classification (Alaggio et al., 2022). PMBCL is thought to arise from thymic (medullary) B cells. FL3B consists of follicle center cells and is characterized by the exclusive presence of centroblasts. The sole distinguishing feature of FL3B (follicular growth) and DLBCL (diffuse growth) is the growth pattern (Koch 2021, Horn 2011). DLBCL and FL3B do not differ significantly with regard to genetics and immunohistochemistry, however rearrangements of the BCL6 gene locus may be less frequent in FL3B compared to DLBCL (Horn 2011).

The pan-B lymphocyte markers include CD20, CD19 and CD79a. CD20 negative NHLs are rare, with a rate of 1–2% of all B cell NHLs. The most common CD20 negative types include plasmablastic lymphoma, primary effusion lymphoma, LBCL arising from HHV8-associated multicentric Castleman's disease, and ALK+ LBCL. However, CD20 positive lymphoma can relapse as CD20 negative lymphoma after CD20 antibody therapy (i.e. rituximab; Hiraga 2009). The frequency of occurrence is unknown. In the literature rates range from 8% till 26% (Marshalek 2022, Prevodnik 2011, Hiraga 2009, Rasheed 2018). In addition, low CD20 expression can also be observed in a part of the newly diagnosed DLBCL patients (11-42%; Johnson et al., 2009; Tokunaga et al., 2014; Choi et al., 2016; Boltežar et al., 2018).

2.1.4. Clinical presentation, diagnosis and stage/prognosis

Patients with DLBCL present with a rapidly enlarging symptomatic mass, most usually nodal enlargement in the neck or abdomen, or, in the case of PMBCL, the mediastinum. Extranodal involvement is common among those presenting with stage I/II disease. Systemic "B" symptoms (i.e., fever, weight loss, drenching night sweats) are observed in approximately 30 percent of patients, and the serum lactate dehydrogenase (LDH) is elevated in over 50% (UpToDate). For prognostic purposes, the International Prognostic Index (IPI) and age-adjusted IPI (aaIPI) should be calculated (Tilly 2015).

DLBCL is diagnosed by a surgical excision biopsy, usually in a lymph node. Pathologic diagnosis is made based on morphology and immunophenotyping. GEP can be used to classify DLBCL in GCB or ABC and cytogenetics to detect abnormalities involving for instance MYC, BCL2 and BCL6 (UpToDate).

DLBCL is curable in approximately half of cases with current therapy, particularly in those who achieve a complete remission with first-line treatment (Crump et al., 2017). Prognosis in DLBCL is highly associated with the International Prognostic Index (IPI) score (Ziepert 2010, Salles 2011) and pathological features (see above). HGBL with MYC and BCL2 and/or BCL6 rearrangements has a more aggressive clinical course compared to DLBCL and a poor response to therapy (Green 2012, Johnson 2012, Rosenthal 2017). PMBCL and FL3B do not differ in clinical course and prognosis from DLBCL (Koch 2021, Lazzarino 1997).

2.1.5. Management

The standard first-line therapy for LBCL and DLBCL as per the recommendations of NCCN and ESMO is R-CHOP (or dose-adjusted R-EPOCH). Substituting vincristine for Polivy leads to a superior PFS in patients with an intermediate- or high-risk prognosis by IPI (Tilly 2021). Although approximately two-thirds of patients survive for 5 years after first line treatment, up to 50% of the patients become refractory to treatment or relapse (Crump et al., 2017). For patients with relapsed or refractory (r/r) DLBCL, standard therapy currently entails salvage chemotherapy with non-cross resistant chemotherapy in second line, followed by autologous hematopoietic stem cell transplantation (ASCT) in medically fit patients (Philip et al., 1995). About half of the patients will have a response sufficient to proceed to ASCT (Gisselbrecht et al 2010, Crump et al 2014).

For DLBCL patients after two or more lines of systemic therapy several therapies are available.

- Chemo-immunotherapy have been a long-standing treatment choice with regimes such as R-GemOX and BR, however these regimens are not associated with long-term disease control/cure. For R-GemOX, responses range between 38% and 66% with a CR rate of 33 till 44% (Cazelles et al., 2021, Mounier 2013, Lopez 2007) and for BR the ORR is 25% with a CR rate of 23%. The duration of response was 17 months till not estimated (NE).
- CAR T-cell therapies, all of which directed at CD19: Yescarta, Kymriah and Breyanzi. ORRs for all treated patients between 54% and 74% have been reported with CR rates between 41% and 54% for all CAR T-cell treated patients. When looking specifically to all patients who were leukapheresed ORR was between 37% and 68% and CR between 28% and 50%. DoRs were observed between 17 to 20 months for Breyanzi at a median follow up (FU) 20 months or were not reached for Yescarta and Kymriah (63 and 24 months FU respectively).For patients not eligible for ASCT the following therapies are approved: Polivy is an anti-CD79b antibody-drug conjugate (ADC). In combination with BR a CR rate of 57%, an ORR of 70% and DOR of 10 months were observed with a median FU of 28 months. A median OS 12 (vs 5 months with BR) has been reported. Minjuvi is a monocloncal antibody against CD19. In combination with lenalidomide, an ORR of 57%, a CR rate of 40% and a DoR 44 months was observed at a median FU time of 35 months.
- Zynlonta is an ADC targeting CD19 authorised by the EC in December 2022. The ORR is 48% with 25% of the patients in CR and a DoR of 10.3 months at a median FU of 7.8 months.
- Pixantrone is a cytotoxic aza-anthracenedione approved for multiply relapsed or refractry aNHL (3^{rd} and 4^{th} line of treatment). The ORR and CR rate at the end of the trial were 40% and 16%. Patients treated with Pixuvri roughly had a 2.5 month longer progression free survival (PFS) and overall survival (OS) compared to single-agent chemotherapy.

Therapies specifically approved for other types of LBCL:

- For HGBL Zynlonta is approved. The ORR was 45% in these patients.
- For PMBCL Breyanzi (ORR 78.6%) and Yescarta (ORR 88%) are approved.
- For FL3B Breyanzi is approved and responses of 66.7% were reported.

There is an unmet need in LBCL patients after two or more lines of systemic therapy to improve treatment outcomes in terms of increasing (duration of) ORR and CR, overcoming resistance to existing therapies and improving safety or providing a different safety profile compared to existing therapies. There is a similar degree of unmet medical need across the disease entities in aggressive NHL, including for patients with HGBL and PMBCL, as well as for patients with FL3B, in which therapies in the relapsed and refractory used are overall similar to those used for DLBCL.

2.2. About the product

Epcoritamab is a humanized IgG1 bispecific antibody that binds to a specific extracellular epitope of CD20 on B cells and to CD3 on T cells. The activity of epcoritamab is dependent upon simultaneous engagement of CD20-expressing cancer cells and CD3-expressing endogenous T cells by epcoritamab that induces specific T-cell activation and T-cell-mediated killing of CD20-expressing cells. Epcoritamab Fc region is silenced for direct immune effector mechanisms, such as antibody-dependent cellular cytotoxicity (ADCC), complement-dependent cellular cytotoxicity (CDC), and antibody-dependent cellular phagocytosis (ADCP).

The pharmacotherapeutic group is antineoplastic agents, Other Antineoplastic agents. The ATC code: not yet assigned.

The claimed indication is "*Tepkinly as monotherapy is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy*."

The proposed posology is epcoritamab (SC) in an initial priming dose of 0.16 mg (Cycle [C]1 Day [D]1), an intermediate dose of 0.8 mg (C1D8), and a full dose of 48 mg at C1D15, C1D22, and thereafter. Then once weekly (QW) during Cycles 2 to 3, once every 2 weeks (Q2W) during Cycles 4 to 9, and once every 4 weeks (Q4W) during Cycle 10 and beyond (until unacceptable toxicity, progressive disease [PD]). The length of one treatment cycle was 4 weeks, i.e. 28 days.

2.3. Type of Application and aspects on development

The applicant requested consideration of its application for a Conditional Marketing Authorisation in accordance with Article 14-a of the above-mentioned Regulation, based on the following criteria:

- The benefit-risk balance is positive.
- It is likely that the applicant will be able to provide comprehensive data.

  The applicant proposed the following specific obligation: In order to confirm the efficacy of epcoritamab in the treatment of relapsed or refractory DLBCL, the MAH should submit the results of the primary efficacy analysis for study GCT3013-05.
- Unmet medical needs will be addressed, as a high unmet medical need still exists for additional novel, effective, and widely available treatment options that can provide meaningful benefit (i.e., improved response rates, manageable/less toxicity) particularly for those who have primary refractory disease and/or disease refractory to multiple lines of therapies (including CAR T-cell therapy), patients with disease transformed from indolent lymphomas, or patients with DH/TH disease, disease with certain chromosomal rearrangements or genetic profiles, and epcoritamab would provide meaningful improvement in efficacy over approved therapies.
- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required.

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as a sterile, single-use, preservative-free, aqueous solution containing 5 mg/mL or 60 mg/mL epcoritamab as active substance. The 5 mg/mL vial is supplied as a 4 mg/0.8 mL concentrate for solution for injection. It is diluted with 0.9% sodium chloride to a final solution for subcutaneous injection for priming and intermediate dose. The 60 mg/mL vial is supplied as a 48 mg/0.8 mL solution for subcutaneous injection, which is a ready-to-use solution that does not need dilution prior to administration (full dose).

Other ingredients are: sodium acetate trihydrate, acetic acid, sorbitol (E420), polysorbate 80, and water for injections.

The product is available in a 2 mL clear type I glass vial, a fluoropolymer-coated rubber stopper and an aluminum cap with flip-off top.

The active substance epcoritamab (INN) is a bi-specific antibody (bsAb) generated by a process called controlled Fab-arm exchange of the two parental antibodies, intermediates 3001d and 3005a. The parental antibodies, 3001d and 3005a, are separately produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology and purified as biological intermediates (BIs).

2.4.2. Intermediates – 3001d and 3005a

2.4.2.1. General Information

The intermediate 3001d (IgG1-CD20-FEAR) is a human IgG1κ antibody targeting B cell antigen CD20, and composed of two heavy chains (HC) and two light chains (LC) with a combined weight of 149 kDa. The two heavy chains are bound to each other by two interchain disulfide bonds, and one light chain is attached to one heavy chain by a single interchain disulfide bond. Each light chain has two intrachain disulfide bonds, and the heavy chains have four intrachain disulfide bonds.

The intermediate 3005a (IgG1-CD3-FEAL) is a humanized IgG1λ antibody targeting T cell antigen CD3, and composed of two heavy chains and two light chains with a combined weight of 149 kDa. The two heavy chains are bound to each other by two interchain disulfide bonds, and one light chain is attached to one heavy chain by a single interchain disulfide bond. Each light chain has two intrachain disulfide bonds, and the heavy chains have four intrachain disulfide bonds.

2.4.2.2. Manufacture, process controls and characterisation

Description of the manufacturing process and process controls

3001d and 3005a biological intermediates are manufactured, tested and released in accordance with Good Manufacturing Practice (GMP). The intermediates 3001d and 3005a are expressed in Chinese Hamster Ovary (CHO) cells. The manufacturing process for the 3001d and 3005a BIs follows the same major steps. Minor differences can be identified with regard to process settings, these are all supported by process characterisation data that are specific for the 3001d and 3005a processes. Cells from a vial of the working cell bank (WCB) are thawed and progressively expanded prior to inoculation of the production bioreactor. Upon completion of the production bioreactor culture, unprocessed bulk is clarified. At the end of cultivation, the unprocessed bulk is tested.

The purification process consists of steps such as chromatography, filtration and removal and inactivation of potential viral contaminants. The processes are designed to capture 3001d and 3005a from the respective clarified harvests, reduce process and product-related impurities, and to produce 3001d and 3005a of the appropriate purity and concentration in the formulation buffer for further manufacture.

A batch of 3001d/3005a biological intermediate is derived from a working cell bank (WCB) vial, production bioreactor and a downstream purification.

Microbial control limits are in place and virus safety was designed into the 3001d/3005a purification processes by including dedicated steps that provide inactivation and removal of potential viruses. Process parameter (PP) ranges and in-process controls (IPCs) are defined and justified as part of the overall control strategy. Reprocessing is allowed in the event of a post-use filter integrity test failure or a breach of system integrity.

Control of materials

Raw materials used in the manufacture of 3001d and 3005a intermediates are either of compendial grade or controlled to ensure the quality and safety of the BI and to maintain the consistency of the manufacturing processand the compositions of media, buffers and solutions are provided in sufficient detail and the applicant is notified in case of changes. The materials are animal and human component free.

The 3001d and 3005a cell banking systems are two-tiered CHO cell bank systems, where the master cell banks (MCB) were used to generate the current and future WCBs. Both cell banks were generated in accordance with GMP requirements using no raw materials of animal or human origin.

The MCBs and WCBs for 3001d and 3005a were tested and characterized including virus testing. Both have been shown to be free from microbial organisms and mycoplasma, confirmed to be of Chinese hamster origin, and suitable for the generation of future WCBs and for manufacturing purposes. The limit of *in vitro* cell age (LIVCA) is defined from thaw of the 3001d and 3005a MCBs. The generation and qualification of future WCBs has been presented and found adequate.

Control of critical steps and intermediates

Classifications of attributes, controls, parameters and ranges used in the dossier are defined. Critical quality attributes (CQAs) were identified. Process characterization has identified that certain process steps can impact the CQAs of the product. The control of these critical steps is important for the control of the CQAs. A critical step is defined as a process step that contains critical process parameters (CPPs) or critical in-process controls (IPCs). The overall control strategy is considered adequate for control of the manufacturing process.

Process validation

The process validation strategy encompasses three stages: process design, process performance qualification (PPQ), and ongoing process verification. The PPQ campaign consisted of multiple consecutive batches and a contingency batch manufactured at the commercial scale and site. The PPQ protocols included prospectively defined acceptance criteria consisting of numerical limits for process parameters and process controls and excursions from the acceptance criteria were evaluated for their impact on product quality.

Data from the PPQ batches and the contingency batch confirm that the manufacturing processes of 3001d and 3005a are in a validated state at the commercial manufacturing site and scale.

The set of supportive process validation includes studies regarding: impurity clearance, in-process product pool hold times, reuse of Protein A resin, and batch uniformity.

An ongoing process verification program will monitor process performance using statistical analysis and trending and limits will be defined when enough data are available; the applicant is reminded that any changes should be applied in accordance with the variation regulation.

Manufacturing process development

During development, 3001d and 3005a both had two versions of processes developed, Process 1 and Process 2. Process 2 is the commercial manufacturing process for 3001d and 3005a. The manufacturing Process 1 was transferred to commercial site (Process 2) to support commercial manufacturing.

Process 1 materials produced under non-GMP and GMP manufacturing conditions for 3001d and 3005a are generally considered comparable. Comparability studies were designed to assess the transfers from the respective Process 1 to Process 2, this is considered adequately demonstrated. The analytical method transfers coinciding with the process transfers are considered adequately performed.

For both intermediates, process characterization was performed to provide process understanding by establishing process parameter criticality, and setting appropriate acceptable ranges for process parameters and acceptance criteria for IPCs using qualified scale-down models. Individual process steps were characterized to determine acceptable ranges for process parameters. Process parameters that impact a CQA are scored to determine the classification (CPP or non-CPP) based on a pre-defined criterion. Overall, the proposed acceptable ranges and process parameter classifications can be considered well supported by development data. The control strategy is considered approvable.

Comparability

An analytical comparability was performed to assess the potential impact on product quality of 3001d and 3005a between Process 1 and Process 2. The comparability study included evaluation of release data, head-to-head analytical testing by selected release tests, extended physicochemical and biological characterization as well as stability study of Process 1 and Process 2 batches. It is concluded that the product quality attributes of 3001d and 3005a are not significantly impacted by the process changes from Process 1 to Process 2. Therefore, the 3001d and 3005a from Process 2 were comparable to that from Process 1. Comparability is considered sufficiently addressed.

Characterization

Characterization of 3001d and 3005a were performed to provide a comprehensive understanding of the biochemical, biophysical, and biological properties of the proteins and a precise description of their quality attributes. State-of-the-art methods were used to evaluate properties that relate to the molecular primary, secondary, tertiary and higher order structures, molar absorption, post-translational modification, size and charge heterogeneity, functional characteristics, immunological properties, and thermal stability. The analytical results from multiple 3001d and 3005a BI batches are consistent with the proposed structures.

Consistent and efficient clearance of process-related impurities is demonstrated.

Size variants of 3001d and of 3005a, high molecular weight species (HMWS) and low molecular weight species (LMWS), have been classified as the product-related impurities. This can be supported. In addition, specific acidic variants of 3005a have been assessed to be product-related impurities due to their impact on the biological activity.

2.4.2.3. Specification, analytical procedures, reference standards, batch analysis, and container closure

Tests were selected based on a detailed understanding of the CQAs of 3001d and 3005a BIs. Identity, purity, protein concentration, and safety of each batch of 3001d and 3005a BIs is assessed and confirmed according to the proposed specification. The BI specification does not include general tests.

Multiple commercial scale batches for both intermediates have been taken into consideration for specification setting and justification, stability data are used to set shelf life limits. The acceptance criteria for purity-indicating attributes, i.e. mass, charge and size heterogeneity, are acceptably set.

Method descriptions for all non-compendial analytical procedures are provided and validations are performed according to ICH Q2(R1). The compendial methods have been verified to demonstrate the suitability for the intended purpose. Analytical procedures are described and validated according to the relevant guidelines.

Batch information for all 3001d BI batches is provided. All batch data were in line with the acceptance criteria at the time of testing except for one. The results for batch release demonstrate a sufficient level of batch-to-batch consistency.

Batch information for all 3005a BI batches is provided. All batch data were in line with the acceptance criteria at the time of testing, except for a Process 1 batch which had out-of-specification results at release. The results for batch release demonstrate a sufficient level of batch-to-batch consistency.

The compendial test methods have been verified in accordance with current editions of pharmacopeias. The non-compendial analytical test methods have been developed and appropriately validated for the release and stability testing of 3001d and 3005a BIs.

Reference standards or materials

The 3001d and 3005a BIs reference standards (RSs) follow a two-tiered approach with a primary RS (PRS) and a working RS (WRS), where the PRS is used to (re)qualify (new) WRSs. The RSs are adequately qualified and considered representative of the commercial product. The PRS and WRS are requalified biannually through the lifetime of the reference standard. Protocols for (re)qualification are provided and considered acceptable.

Container closure system

3001d and 3005a BIs are stored in single use sterile bags. The bags meet the relevant requirements with regard to biological activity, microbial aspects, transmissible spongiform encephalopathy (TSE) and compatibility.

2.4.2.4. Stability

Stability studies are being conducted on all 3001d and 3005a BIs Process 1 and Process 2 GMP batches manufactured to date in accordance with ICH stability guidelines. The stability studies are performed using containers from the same materials as the 3001d /3005a BI container closure system but downscaled in size. At the proposed long-term storage conditions, the stability-indicating parameters show no significant effect. Under the accelerated and stressed storage conditions, the 3001d and the 3005a BIs shows partial degradation, which is not unexpected for proteins under these storage conditions. Analytical comparability has been established between 3001d / 3005a batches manufactured by Process 1 and Process 2 and the Process 1 batches are therefore used as supportive data for defining the shelf life of 3001d / 3005a BIs.

2.4.3. Active substance

2.4.3.1. General information

The active substance, epcoritamab (INN), is a bi-specific IgG1λκ antibody (bsAb) generated by a process called controlled Fab-arm exchange of the two parental antibodies, 3001d and 3005a. It is composed of two heavy chains and two light chains with a combined weight of 149 kDa. The two heavy chains are bound to each other by two interchain disulfide bonds, and one light chain is attached to one heavy chain by a single interchain disulfide bond. Each light chain has two intrachain disulfide bonds, and the heavy chains have four intrachain disulfide bonds.

Epcoritamab carries inertness mutations to silence Fc-mediated effector functions. It has characteristics typical of a human IgG1 antibody, including normal neonatal Fc receptor (FcRn) binding and in vivo stability.

Epcoritamab simultaneously binds to CD3 on T-cells and CD20 on malignant B-cells, inducing CD20-specific T-cell activation and T-cell-mediated cytotoxicity.

2.4.3.2. Manufacture, process controls and characterisation

Description of manufacturing process and process controls

Epcoritamab active substance is manufactured by Rentschler Biopharma Inc. (Milford, MA, USA) in accordance with GMP. Epcoritamab active substance manufacturing consists of thawing and pooling the biological intermediates, 3001d and 3005a, reduction and re-oxidation as well as a purification step. Multiple ultra/diafiltratration (UF/DF) steps are included in the process to remove process-related impurities and to concentrate the protein. Polysorbate 80 (PS80) is then added and the protein concentration is adjusted prior to filling into bags and freezing. All steps are performed at ambient temperature (18°C to 25°C), unless specified otherwise. All UF/DF membranes are single use.

The scale of the manufacturing process is defined by the combined amounts of biological intermediates 3001d and 3005a that goes into each batch of epcoritamab active substance. For one epcoritamab active substance batch, multiple batches of the individual BIs, 3001d and 3005a can be used. All BI batches used for epcoritamab active substance manufacturing must comply with the acceptance criteria for release.

One filtered intermediate with a hold time is defined as justified by a stability assessment. Microbial control limits are in place for the in-process intermediates are tested (pre-filtration) for bioburden and bacterial endotoxins. Virus safety is controlled at the level of the BI's as no cells are used for the manufacture of epcoritamab active substance. Lifecycles of the chromatography resin is qualified, all membranes and filters are single-use. Process parameter (PP) ranges and in-process controls (IPCs) are defined and justified as part of the overall control strategy. Reprocessing is allowed in the form of refiltration exclusively in the event of a post-use filter integrity test failure or a breach of system integrity.

Control of materials

Sufficient information on raw materials used in the active substance manufacturing process has been submitted. Raw materials used in the manufacture of epcoritamab active substance are either of compendial grade or controlled to ensure the quality and safety of the active substance and to maintain the consistency of the manufacturing process. No human or animal derived materials are used in the active substance manufacturing process.

Control of critical steps and intermediates

Classifications of attributes, controls, parameters and ranges used in the dossier are defined. Critical quality attributes (CQAs) were identified. Process characterization has identified that certain process steps can impact the CQAs of the product. The control of these critical steps is important for the control of the CQAs. A critical step is defined as a process step that contains critical process parameters (CPPs) or critical in-process controls (IPCs). If the acceptable criteria for a CPP or critical IPC are exceeded, a non-conformance is initiated, an investigation is performed and a batch could be rejected. The overall control strategy is considered adequate for control of the manufacturing process.

Process validation

The process validation strategy encompasses three stages: process design, process performance qualification (PPQ), and ongoing process verification. The PPQ campaign consisted of multiple consecutive batches manufactured at the commercial scale and process. The PPQ protocols included prospectively defined acceptance criteria consisting of numerical limits for process parameters and process controls and excursions from the acceptance criteria were evaluated for their impact on product quality. All PPQ lots met the proposed commercial active substance release specification acceptance criteria and demonstrated consistent performance of the active substance manufacturing process. The set of supportive process validation includes studies regarding: impurity clearance, in-process product pool hold times, reuse of resin, and batch uniformity.

An ongoing process verification program will monitor process performance using statistical analysis and trending and limits will be defined when enough data are available.

Manufacturing process development

During development, epcoritamab active substance was initially produced at smaller scale at clinical manufacturing site (Process 1) for clinical use. Polysorbate 80 (PS80) was added to the active substance formulation from Process 1 batches and onwards for GMP batches manufactured with both Process 1 and Process 2. The manufacturing process was later transferred to the commercial manufacturing site (Process 2). In addition, it was decided to manufacture the 5 mg/mL as part of the finished product process. The analytical methods were also transferred along with the process transfer from Process 1 to Process 2.

Process 1 material and Process 2 are generally considered comparable. A comparability study was designed to assess the transfer from Process 1 to Process 2, this is considered adequately demonstrated. The analytical method transfer coinciding with the process transfer is considered adequately performed.

Process characterization was performed to provide process understanding by establishing process parameter criticality, and setting appropriate acceptable ranges for process parameters and acceptance criteria for IPCs using qualified scale-down models, while the reduction and re-oxidation step are considered scale-independent. Individual process steps were characterized to determine acceptable ranges for process parameters with a combination of a multivariate approach using Design of Experiments (DoE), univariate experiments, or worst-case experiments. Process parameters that impact a CQA are scored to determine the classification (CPP or non-CPP) based on a pre-defined criterion. Overall, the proposed acceptable ranges and process parameter classifications can be considered well supported by development data. Worst-case studies confirm the criteria set during process characterization. Studies are presented that demonstrate the adequacy of refiltration and resin lifetime as laid down in CTD section S.2.2. The control strategy is considered approvable.

Characterization

Characterization of epcoritamab was performed to provide a comprehensive understanding of the biochemical, biophysical, and biological properties of the protein and a precise description of its quality attributes. State-of-the-art methods were used to evaluate properties that relate to the molecular primary, secondary, tertiary and higher order structures, molar absorption, post-translational modification, size and charge heterogeneity, functional characteristics, immunological properties, and thermal stability. The analytical results from multiple Process 2 batches are consistent with the proposed structure.

The biological function of epcoritamab is binding to both CD3 and CD20, which has been characterized for batch 1079437. Co-engagement by epcoritamab of CD3 on T cells and CD20 on malignant B cells and resulting (CD4- and CD8-positive) T cell activation, and T cell-mediated cytotoxicity of CD20-expressing B cells is demonstrated by three different bioassays.

A deeper understanding of epcoritamab and the identification of CQAs has been obtained by isolation and characterization of size and charge variants, and forced degradation studies. Epcoritamab can be considered relatively stable, and significant reductions in biological activity are obtained for material that was subjected to testing.

Consistent and efficient clearance of process-related impurities is demonstrated, which are present at low levels and consistent between batches. The process-related impurities in the biological intermediates 3001d and 3005a that can be carried into the epcoritamab active substance are controlled at the 3001d and 3005a manufacturing stage.

The batch analysis results indicated the levels of product-related impurities are consistent across commercial process batches and the process is well controlled and robust.

A summary of the risk evaluation for introducing leachables into epcoritamab finished product has been provided. The theoretical extractable concentrations are not a concern for patient safety. The information provided is sufficient and does not raise any further issues.

2.4.3.3. Specification

Identity, quality and purity of each batch of epcoritamab active substance is assessed and confirmed according to the proposed specification. The following tests are included in the active substance specification: general tests, identity, purity, potency, protein, and safety. Tests were selected based on a detailed understanding of the CQAs of epcoritamab active substance. The active substance specification does not include a general test for osmolality, tests for process-related impurities, and oligosaccharide profiling. Osmolality is sufficiently controlled at the level of the finished product and the process-related impurities are consistently present at sufficiently low levels. Residual host cell proteins (HCP) is considered sufficiently controlled at the level of the BI's and additional testing the active substance level is not necessary. A replacement of the current method for charge heterogeneity for release and stability testing of epcoritamab active substance will be implemented (**recommendation**).

Commercial scale epcoritamab active substance batches have been taken into consideration for specification setting and justification, and stability data are used to set shelf life limits. The calculated clinical coverage of the proposed epcoritamab active substance specification acceptance criteria has been acceptably assessed.

Analytical methods

Method descriptions for all non-compendial analytical procedures are provided and validations are performed according to ICH Q2(R1). The compendial methods have been verified to demonstrate the

suitability for the intended purpose. Analytical procedures are described and validated according to the relevant guidelines.

The biological activity of epcoritamab is determined in a surrogate T-cell activation assay and the biological activity of epcoritamab is reported as % relative potency relative to a reference standard.

Batch analysis

Batch information for all epcoritamab active substance 60 mg/mL batches is provided. All batch data were in line with the acceptance criteria at the time of testing. The results for batch release demonstrate a sufficient level of batch-to-batch consistency.

Reference materials

The epcoritamab active substance reference standards (RSs) follow a two-tiered approach with a primary RS (PRS) and a working RS (WRS), where the PRS is used to (re)qualify (new) WRSs. The RSs are adequately qualified and considered representative of the commercial product. The PRS and WRS are requalified biannually through the lifetime of the reference standard. Protocols for (re)qualification are provided and considered acceptable.

Container closure system

Epcoritamab active substance is stored in single use sterile bags. The bags meet the relevant requirements with regard to biological reactivity, microbial aspects, TSE and compatibility.

2.4.3.4. Stability

Stability studies are being conducted on epcoritamab active substance batches manufactured to date in accordance with ICH stability guidelines. The stability studies are performed using containers from the same materials as the epcoritamab active substance container closure system but downscaled in size. Analytical comparability has been established between batches produced by Process 1 and by Process 2 at the commercial facility. At the proposed long-term storage conditions, the stability-indicating parameters show no significant effect for 48 months. Under accelerated condition, little to no notable change was observed. Under stressed storage conditions, the epcoritamab active substance shows partial degradation, which is not unexpected for proteins under these storage conditions.

The stability results indicate that the active substance is sufficiently stable and justify the proposed shelf life in the proposed container.

2.4.4. Finished medicinal product

2.4.4.1. Description of the product and pharmaceutical development

Epcoritamab finished product is a sterile, preservative-free liquid supplied in a single dose vial.

The epcoritamab finished product 5 mg/mL is a concentrate for solution for injection. Each vial contains 4 mg of epcoritamab in 0.8 mL. It is diluted in sterile 0.9% sodium chloride to a final solution for subcutaneous injection.

The epcoritamab finished product 60 mg/mL is a solution for subcutaneous injection. Each vial contains 48 mg of epcoritamab in 0.8 mL. Other ingredients are: sodium acetate trihydrate, acetic acid, sorbitol (E420), polysorbate 80, and water for injections.

Each vial contains an overfill ensuring an extractable volume of ≥0.8 mL/vial. Epcoritamab finished product of both presentations have a pH of 5.5.

The container closure system consists of a 2 mL clear type I glass vial, a fluoropolymer-coated rubber stopper and an aluminium cap with flip-off top.

There are no overages included in the manufacture of the finished product. An overfill volume was applied to ensure that 0.8 mL can be extracted from the vial. Supportive data for the proposed overfill has been provided.

Both presentations of epcoritamab finished product are intended for subcutaneous injection. The quality target product profile (QTPP) includes the criteria for identity, potency, purity, and physicochemical properties as these may affect the efficacy and safety of the finished product.

The applicant presented the formulation development of the finished product, as well as results of a formulation screening study using a Design of Experiment (DoE) approach, a formulation robustness study also using a DOE approach, a DOE study to address the impact from freeze-thaw and a DOE study to address the impact from agitation stress. The robustness of the commercial formulation has sufficiently been shown. Repeated freeze-thaw cycles and agitation stress studies did not reveal any impact on epcoritamab physicochemical quality attributes. Photostability studies demonstrate that the finished product is light sensitive under ICH light conditions. Therefore, the finished product should be stored protected from light.

The initial clinical manufacturing process for epcoritamab finished product was developed, described as Process 1. During development, the finished product manufacturing process was transferred to the commercial manufacturing facility and scaled up, described as Process 2. Finished product batches manufactured using Process 1 as well as a number of finished product batches using the full scale (commercial) process were used in the clinical studies GCT3013-01 and GCT3013-04. Process changes to support commercial manufacturing (Process 2) have been adequately justified. To assess potential impact on product quality, release data and stability profiles of finished product batches manufactured with Process 1 and Process 2 were compared. All release results were comparable and met the comparability acceptance criteria. Overall, the stability profiles after storage for Process 2 batches are comparable to what has been observed for historical batches. On request, the applicant provided also results of additional characterization tests. These results further substantiate that process 1 and process 2 finished product batches are highly comparable.

The finished product control strategy is based on CQA assessment and the manufacturing process impact on epcoritamab CQAs controlled during finished product manufacturing. In accordance with ICH guidelines the criticality of each attribute was evaluated based on impact and uncertainty level. The impact level was determined based on the potential impact on safety and efficacy of the product while the uncertainty level was determined based on the information and product understanding available at the time of the risk analysis (e.g., prior knowledge, analytical characterization and available literature). The finished product control strategy is part of an integrated control strategy which summarizes the complete list of epcoritamab CQAs and the stage where each CQA is controlled, including the 3001d and 3005a biological intermediates as well as epcoritamab active substance stages. Within each stage of manufacture, the CQAs potentially impacted by that stage were evaluated in a process impact assessment. Control ranges for process parameters were derived from process characterization studies or based on historical data and/or experience with comparable development programs. The identified critical process parameters (CPPs) and their control within established control ranges are one important control element of the control strategy. Overall, the approach of the applicant can be endorsed.

The primary packaging components used for epcoritamab finished product have been selected to ensure overall quality throughout the shelf life. The vial is a 2R type I glass vial suitable for liquid injectables. The stopper is made of bromobutyl rubber with a fluoropolymer foil. The closed vials are sealed with an aluminum/plastic flip-off cap. The compatibility of the container closure system has been demonstrated by long term stability studies of representative finished product batches.

It was determined that the (diluted) finished product is compatible with a range of non-polar and weakly polar materials, representing commonly used ancillaries for preparation, dilution and subcutaneous administration of epcoritamab finished product. Filtration of the product is not needed.

The in-use stability study supported the in-use storage (24 hours at 2-8°C, whereof up to 12 hours may be at room temperature) when the preparation of the finished product is taking place in controlled and validated aseptic conditions.

2.4.4.2. Manufacture of the product and process controls

Batch release of the finished product is performed by AbbVie S.r.l. (Campoverde, Italy) in accordance with GMP.

The exact batch size is defined by the volume of the active substance available at the time of manufacture. Finished product manufacturing process consists of the thawing of active substance, compounding of bulk finished product, sterile filtration, aseptic filling, and visual inspection, All steps have been described in sufficient detail and acceptable ranges for CPPs and non-CPPS are provided. Process parameters and associated ranges are sufficiently justified by the studies described in the section on manufacturing process development section. Hold times and process times are defined and have been justified by validation studies performed during process development.

A critical step is defined as a process step that contains CPPs or critical in-process controls IPCs. The data in the development section support the CPPs and critical IPCs or the CPPs/CIPCs are in line with current guidance and common practice.

Process Performance Qualification (PPQ) was performed by manufacturing consecutive finished product batches at commercial scale. A bracketing approach was used. This is to conform to the EMA scientific advice (EMA/CHMP/SAWP/521927/2020) provided in October 2020. Process and hold times were not challenged, which is acceptable as these were already validated during manufacture of the primary (pre-PPQ) batches. Homogeneity of the formulation solution, formulated finished product solution and during filling (begin, middle, end of fill) were verified. Relevant quality attributes were determined in various steps of the manufacturing process and no changes were observed. In conclusion, multiple consecutive PPQ finished product batches were successfully manufactured. All process parameters were applied within the validation limits, and the pre-determined criteria for in-process controls and release specification were met for all batches. It is therefore demonstrated that the manufacturing process is capable of consistent production of epcoritamab finished product that meets the expected quality.

2.4.4.3. Product specification

Finished Product specifications include tests for appearance, identity, purity and impurities, potency, content, general characteristics, and safety. The proposed panel of release tests is considered adequate to confirm the quality of the finished product provided. The applicant has adequately justified the absence of a test for protein oxidation.

Analytical methods

The analytical procedures include both compendial and non-compendial methods. The compendial methods were verified for their intended use in accordance with current editions of pharmacopeia's. The non-compendial methods used for finished product are the same methods as those for the active substance release testing and the description and validation of these methods is provided in the active substance section. Proposed acceptance criteria are based on published limits (e.g. Pharmacopeia), a target limit approach based on the design or formulation robustness studies, a stability limit approach based on tolerance interval statistical analysis of release data in combination with prediction of shelf life changes, or an empirical limit approach. On request, the shelf-life limits for mass heterogeneity and charge heterogeneity have also been clinically justified. In addition, the applicant is recommended to implement a method for release and stability testing of finished product for charge heterogeneity (**recommendation**).

Batch analysis

Batch analysis data for epcoritamab finished product are provided for 5 mg/ml batches and 60 mg/ml batches. All batch analysis data comply with the specification at time of release and are considered sufficiently consistent.

A risk assessment was performed to evaluate the potential presence of nitrosamine impurities in the finished product. The assessment concluded that the finished product manufacturing process is not at risk for the formation or introduction of nitrosamine impurities.

A risk evaluation according to the ICH Q3D guideline was performed to assess the risks for introducing elemental impurities in epcoritamab finished product. To support the elemental impurities risk assessment, multiple batches were screened for a total of 10 elements. None of the elements were detected above the practical detection limit.

Reference materials

The reference standard used for epcoritamab finished product testing is the same as used for the epcoritamab active substance.

Container closure system

The container closure system for both presentations consists of a 2 mL clear type I glass vial, a fluoropolymer-coated rubber stopper and an aluminium cap with flip-off top. Vial and stopper comply with Ph. Eur. quality standards.

2.4.4.4. Stability of the product

A shelf life of 24 months at 2°C to 8°C is proposed. This is supported by long term data (2 – 8°C) of a number of 5 mg/ml and 60 mg/ml batches from Process 1 and Process 2. Stability data were supplied for both vials stored in the upright position and vials stored in the inverted position.

During long term storage (2-8°C) no notable changes were observed for appearance, mass, charge and size heterogeneity, biological activity, protein concentration, pH, polysorbate 80 and subvisible particles. Container closure integrity met the acceptance criteria.

At accelerated condition slight change in the mass, size and charge heterogeneity was observed. At stress condition these changes were more pronounced and a decrease of potency was also observed at this condition. No notable changes were observed for the other attributes under accelerated or stress condition.

Photostability studies demonstrate that the finished product is light sensitive under ICH light conditions. Therefore, the product should be stored protected from light.

In conclusion, real-time/real temperature data are available for multiple 5 mg/ml batches and 60 mg/ml batches (process 1). These batches are considered sufficiently representative of that will be used for commercial manufacturing (process 2) and show comparable stability trends at long term storage condition as primary (process 2) stability batches. Sufficient results are now available in support of the proposed storage conditions and expiration dating period.

The proposed finished product shelf life of 2 years at 2-8°C is considered acceptable.

The SmPC states the in-use stability requirements according to the guideline text: *Chemical and physical in-use stability has been demonstrated for 24 hours at 2-8°C including up to 12 hours at room temperature (20-25°C).*

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

2.4.4.5. Adventitious agents

The intermediates 3001d and 3005a are produced using CHO host cell lines. No animal-derived raw materials are used in the manufacture.

The adventitious agent safety evaluation for the 3001d and 3005a biological intermediates manufacturing process covers non-viral and viral adventitious agents. An integrated approach including prevention, detection, and removal is followed to ensure viral safety. The prevention aspect involves careful sourcing of raw materials to prevent adventitious agents and BSE/TSE agents from entering upstream processes. Virus and other adventitious agents were tested for unprocessed bulk harvest and the MCB, WCB, and End of Production Cells (EPC) at the limit of in vitro cell age for both 3001d and 3005a in accordance with the ICH Guideline Q5A(R1). The virus clearance study demonstrated that the 3001d and 3005a manufacturing processes employ a robust and orthogonal virus clearance for a wide range of viruses.

The effectiveness of the 3001d and 3005a purification process to remove or inactivate viruses has been studied, which provided a quantitative estimate of the level of virus reduction or inactivation across different steps of the purification process.

Overall, an integrated approach to ensure adventitious agent safety was demonstrated for the manufacture processes of 3001d, 3005a and epcoritamab active substance.

The applicant has calculated the estimated retrovirus particles per dose of 48 mg 3001d or 3005a based on the cumulative minimum reduction factors.

2.4.5. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

During the procedure questions were identified (relating to intermediate and active substance process descriptions, comparability, characterisation, and active substance/finished product process validation specification and stability) which have been adequately addressed.

At the time of the CHMP opinion, a minor unresolved quality issue remains. This issue has no impact on the Benefit/Risk ratio of the product and concerns the replacement of the current method for charge heterogeneity with a method for release and stability testing of active substance and finished product.

This point is put forward and agreed as recommendation for future quality development.

2.4.6. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.4.7. Recommendation for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following point for investigation:

- to implement a method for release and stability testing of active substance and finished product for charge heterogeneity.

2.5. Non-clinical aspects

2.5.1. Introduction

Epcoritamab is a full-length IgG1 bispecific antibody recognizing CD3 and CD20. It triggers potent T-cell-mediated killing of CD20-expressing cells and is indicated as monotherapy for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL). Mutations were introduced in the Fc domain of the parental antibodies to obtain a silenced Fc region that does not bind to IgG Fc receptors (FcγR) and the complement component C1q leading to reduced CDC, and to retain the binding to FcRn in order to maintain a relatively long plasma half-life. Research grade batches of epcoritamab (DuoBody-CD3xCD20) used in non-clinical pharmacology studies were comparable to clinical grade batch (NBL0190-29-01) used in the pivotal GLP toxicity study.

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

In vitro studies showed that epcoritamab binds in a concentration-dependent manner to cell surface-expressed CD3 on freshly isolated, CD20-negative, human healthy donor T cells with EC50 of 4.73 nM. EC50 values were in the same range for CD4+ or CD8+ primary T cells. The affinity (dissociation constant, K_D) of epcoritamab for soluble CD3ε was 12.5 nM. Epcoritamab was shown to bind in a concentration-dependent manner to cell surface-expressed CD20 on human Burkitt´s lymphoma B cells (Daudi cells) with the EC50 of 10.40 nM. EC50 values of the same range were observed using CD20-transfected, CD3-negative HEK-CD20 cells. Epcoritamab was capable of simultaneously binding

to CD3-expressing T cells (both CD4+ and CD8+) and CD20-expressing B cells in whole blood in concentration-dependent manner. Concentrations at which T-cell activation and cytotoxicity by epcoritamab were first observed (EC20) were in the very low picomolar range and those at which half-maximal T-cell activation and cytotoxicity were observed (EC50) were in the low picomolar range (Table 14). Epcoritamab could induce potent cytotoxicity when binding was suboptimal.

Table 1: In vitro assays with Daudi target cells and PBMC- T cells as effector cells

In-vitro cellular system	Effector cells	E:T ratio	Average EC20		Average EC50		No. of donors
			pg/ml [SD]	pM [SD]	pg/ml [SD]	pM [SD]	
T-cell activation CD69 upregulation (% CD69+)	CD4+ T cells	5:1	5 [7]	0.033 [0.047]	11 [20]	0.073 [0.133]	10
	CD8+ T cell	5:1	5 [5]	0.033 [0.033]	25 [20]	0.167 [0.133]	10
T-cell activation CD25 upregulation (% CD25+)	CD4+ T cells	5:1	4 [4]	0.027 [0.027]	21 [24]	0.140 [0.160][1]	10/11
	CD8+ T cell	5:1	12 [12]	0.080 [0.080]	76 [65]	0.507 [0.433][1]	10/11
T-cell activation PD-1 upregulation (% PD-1+)	CD4+ T cells	5:1	7 [10]	0.047 [0.067]	68 [70]	0.453 [0.467]	10
	CD8+ T cell	5:1	35 [34]	0.233 [0.227]	360 [264]	2.400 [1.760]	10
T-cell cytotoxicity- ^{51}Cr release	T cells	10:1	189 [539]	1.26 [3.59]	634 [1165]	4.227 [7.769]	20
	CD4+ T cells	10:1	190 [307]	1.27 [2.05]	638 [604]	4.251 [4.029]	6
	CD8+ T cells	10:1	17 [21]	0.113 [0.140]	126 [119]	0.841 [0.792]	5
T-cell cytotoxicity- Flow cytometry	T cells	2:1	5 [4]	0.033 [0.027]	39 [22]	0.260 [0.147]	11

CD = cluster of differentiation; EC20 = concentration at which 20% of the maximum effect is observed; EC50 = concentration at which 50% of the maximum effect is observed; E:T =effector cell to target cell; SD = standard deviation;

In vitro cross-reactivity of epcoritamab to CD20 from non-human species has been evaluated by using HEK293F cell lines transfected with human, cynomolgus monkey, dog, rabbit, pig, rat or mouse CD20. Human expressed CD20 was used as positive control. Only CD20 from cynomolgus monkeys and rabbits interacted with epcoritamab, showing dose-dependent binding. The binding EC50 values of epcoritamab to cynomolgus monkey and human CD20 were comparable. Similarly, comparable binding affinities were determined for human and cynomolgus monkey CD3 using T-cell lines (Jurkat [human] and HSC-F [cynomolgus monkey]). No cross-reactivity to CD3 from other non-human species is expected according to submitted literature data (Conrad 2007, Cytometry). It is acceptable that epcoritamab is not likely to bind to CD3 of other species than cynomolgus monkeys. Based on this, it is considered well justified that cynomolgus monkey is the only relevant nonclinical species to predict epcoritamab PD/PK response when tested in humans.

Three mutations were introduced into the Fc region to abrogate Fc-mediated effector functions in order to render epcoritamab highly selective towards cytotoxic CD3-expressing T-cells. The inertness of the Fc region of the epcoritamab was demonstrated in *in vitro* binding and functional assays. *In vitro* binding studies showed that epcoritamab did not bind to human FcγRI, FcγRIIb, FcγRIIa-131H/R and FcγRIIIa-158F/V constructs, in contrast to IgG1-ctrl and IgG1-CD20-K409R, which do not contain the inertness mutations in the Fc region. Epcoritamab showed *in vitro* minimal C1q binding and reduced capacity to induce CDC in CD20-positive cells at clinically relevant concentrations (7% relative to IgG1-CD20).

Binding to FcRn is not affected by the mutations in the Fc region. Epcoritamab showed dose-dependent binding to human FcRn at pH 6.0 (Kd 36.7 nM) that was comparable to wild type IgG1, whereas no

binding was observed at pH 7.4. In support to this, plasma concentrations over a timeframe of 21 days and plasma clearance rate of surrogate test compounds, IgG1-CD3*-F405L-FEA and IgG1-CD3*-F405L, were comparable in immunodeficient tumour-free mice, indicating that target independent plasma clearance of antibodies is not affected by the Fc inertness mutations.

Cytotoxicity

The capacity of epcoritamab to induce target mediated T-cell activation, T-cell proliferation and T-cell mediated cytotoxicity was investigated in several *in vitro* studies in the presence of CD20-expressing cells (endogenous human B cells and several cell lines derived from different types of B-cell lymphoma, including DLBCL subtype). CD20-expressing cells were cultivated with CD3+ T cells (Jurkat T cells or freshly isolated human peripheral blood T cells) and different concentrations of epcoritamab. It was shown that epcoritamab mediated dose-dependent activation of CD4+and CD8+ T cells in the presence of CD20-expressing Daudi cells as well as potent dose-dependent T-cell-mediated cytotoxicity towards Daudi cells, with the CD8+ T cells apparently more potent than CD4+ T cells (Table 1). Moreover, CD8+T-cell-mediated cytotoxicity was reached after 3 h, whereas cytotoxicity mediated by CD4+ T cells was observed only after 24 h. Similar results were obtained in the panel of CD20+ cell lines derived from different subtypes types of B-cell lymphoma origin, including activated B-cell-diffuse large B-cell lymphoma (ABC-DLBCL), mantle cell lymphoma (MCL), germinal center B-cell-diffuse large B-cell lymphoma (GCB-DLBCL). There was no relation between CD20 cell surface expression and cytotoxicity. Epcoritamab could induce potent cytotoxicity when binding was suboptimal. Further, in co-cultures of T- and B-cells or in PBMCs containing T- and B-cells, the B-cell killing was completely dependent on the binding of both CD3 and CD20 by the epcoritamab, because the absence of a CD20-binding arm (DuoBody-CD3xctrl) or absence of a CD3 binding arm (DuoBody-ctrlxCD20) abrogated T-cell-mediated killing of CD20 expressing B cells. Target dependent cytotoxicity was confirmed by using target cells not expressing CD20 such as SK-BR-3 breast cancer cells. The viability of SK-BR-3 cells not expressing CD20 remained unaffected at epcoritamab concentrations up to 1mg/ml. Further, the capacity of epcoritamab to induce cytotoxicity in primary malignant cells was analysed *ex-vivo* in a panel of lymph node and bone marrow biopsies (total of 37 samples) obtained from patients with different malignancies, including DLBCL, FL and MCL, in the presence of healthy donor- or patient-derived PBMCs. Epcoritamab induced dose-dependent response of DLBCL, FL and MCL patient samples, in the presence of healthy donor PBMCs while patient-derived T cells were functionally able to mediate epcoritamab-induced cytotoxicity but was dependent on the number of T cells present in the samples.

Epcoritamab was functionally active in PBMC populations of cynomolgus monkey origin, where dose-dependent induction of T-cell activation (EC50 values of 0.1273 pM for CD4+ and 0.0347 pM for CD8+ T-cells) and cytotoxicity (EC50 value of 0.0093 pM) were observed. Based on comparable binding of epcoritamab to human and cynomolgus monkey CD3 and CD20 and comparable *in vitro* pharmacology of epcoritamab in human and cynomolgus monkey PBMC populations, cynomolgus monkey was selected as the relevant species for nonclinical safety evaluation of epcoritamab.

The influence of the standard first-line therapies (R-CHOP- rituximab, cyclophosphamide, hydroxydaunorubicin, oncovin and prednisone) in DLBCL on the efficacy of epcoritamab was studied *in vitro* (CHOP) as well as *ex-vivo* and *in vivo* (rituximab). *In vitro* T-cell activation and T-cell-mediated cytotoxicity assays were performed after pre-incubation of T cells (isolated from healthy donors) or B cells (human NHL B-cell line SU-DHL-4) with the CHOP components. The results showed that doxorubicin dose-dependently reduced T-cell viability and strongly affected epcoritamab-induced CD4+ and CD8+ T-cell activation while oncovin and prednisone slightly affected T-cell activation. Nevertheless, epcoritamab-induced T-cell-mediated cytotoxicity of B cells was not strongly affected in the presence of CHOP, except at high doxorubicin concentration. An *in vivo* study was performed in NOD-SCID mice inoculated with a mixture of human unstimulated PBMCs and Raji-luc cells. The presence of up to 10 mg/kg circulating rituximab (IgG1-RTX-FEAR with silenced Fc-mediated effector

functions to ensure that anti-tumour activity observed in this study could be attributed to epcoritamab and not rituximab), did not hamper anti-tumour activity of epcoritamab towards malignant B cells *in vivo*. This was also confirmed by studies *ex-vivo* using biopsies derived from B-NHL patients previously treated by rituximab. In conclusion, in the experimental set-up reported by the applicant, no clinically relevant effect of first-line therapeutics on the effect of epcoritamab were seen. However, if these experiments are representative of the clinical situation is not completely clear, as long lasting effects on B-cells and bone marrow are possible after treatment with R-CHOP, even when the components are no longer in circulation.

In vivo efficacy

The anti-tumour activity of IV administered epcoritamab was assessed *in vivo* using three different B-cell lymphoma xenograft (CDX) models and one DLBCL PDX model and different types of humanized mice. Epcoritamab delayed growth of CD20+ tumour in all tested mouse models, however not always in a dose-dependent manner. Epcoritamab also delayed tumour growth in mice with a human immune system (HIS) inoculated IV with Daudi- and SC with Raji cells, respectively, whereas bsAb-CD3xctrl, that lacks the CD20-specific arm, did not. Further, epcoritamab, but not bsAb-CD3xctrl, also significantly reduced the number of human B cells in the peripheral blood of mice, as was determined on day 9. Interestingly, bsAb-ctrlxCD20 that lacks the CD3-specific arm, induced some anti-tumour activity and some human B-cell depletion in peripheral blood in Raji-luc xenograft model using BRGS-HIS mice, however this treatment did not significantly prolong survival of the mice compared to PBS group. Peripheral blood human T-cell numbers were affected by epcoritamab treatment, but not by treatment with DuoBody-CD3xctrl or DuoBody-ctrlxCD20. On day 4 (one day after the first administration of epcoritamab), T-cell numbers appeared to be decreased compared to the PBS-treated group at the same day, an observation that was significant for CD4+ T cells in mice treated with 0.1 or 1 mg/kg. Five days later, on day 9, T-cell numbers were increased compared to the PBS-treated group, an observation that was significant for CD8+ T cells in mice treated with 1 mg/kg epcoritamab. After day 9, T-cell numbers returned to pre-treatment values, and did not change in response to the later administrations of epcoritamab. In Burkitt's lymphoma CDX model (Raji cells) using NSG mice with human immune system, low doses (0.05 mg/kg and 0.5 mg/kg) appear to have a delayed but strong effect, whereas high dose (5 mg/kg) has an immediate but less strong effect.

The anti-tumour activity of IV administered epcoritamab was also evaluated *in vivo* in HIS mice that were implanted SC human tumour biopsy material (DLBCL patient-derived xenograft model). The model closely relates the target indication. Epcoritamab effectively delayed tumour growth only at the highest tested dose (5 mg/kg) which was reflected in prolonged progression-free survival. Efficacy appears to be transient however, as tumour volume increases before the last dose is given. There were three sudden deaths in mice treated with 5 mg/kg epcoritamab. The early deaths were associated with body weight loss > 20%, and the relationship to epcoritamab treatment remained unclear but is likely, and could be related to cytokine release.

Pharmacologic effects consistent with the mode of action of epcoritamab, including depletion of peripheral blood B cells and cytokine release were also observed in the toxicity study in cynomolgus monkeys *in vivo*. Single injection of epcoritamab, administered IV or SC, induced a dose-dependent depletion of B cells from peripheral blood and lymph nodes. B-cell depletion was reversible at all dose levels. The high SC single dose of 10 mg/kg showed longer recovery time of the B cells in comparison to the lower dose of 1 mg/kg. Efficiency of B-cell depletion was comparable after SC and IV administration of epcoritamab (see toxicology section).

2.5.2.2. Secondary pharmacodynamic studies

The immunogenicity of humanised CD3-specific Fab arm and the Fc region of epcoritamab has been evaluated by in silico and in vitro cell-based modelling approaches, i.e. in silico EpiMatrix system and in vitro EpiScreen cell-based assay. The immunogenicity of the CD3 arm and Fc region of IgG1-CD3-FEAL is predicted to be low and in the range of other therapeutic antibodies that have been found in the clinic to be non-immunogenic. The use of in silico EpiMatrix system and in vitro EpiScreen cell-based assay is considered of high impact for the estimation of risk for clinical immunogenicity since the predictivity of animal studies for evaluation of immunogenicity in humans is considered low [EMEA/CHMP/BMWP/14327/2006 Rev 1].

2.5.2.3. Safety pharmacology programme

No specific safety pharmacology studies have been conducted with epcoritamab. Effects on the central nervous, respiratory, and cardiovascular systems were evaluated in the pivotal repeat-dose toxicity study in cynomolgus monkeys. Heart rate and RR, PR, QRS and QT intervals on Day 8 and 22 (repeated IV dosing) or Day 1 (single IV or SC dosing) were unaffected by treatment. Slightly uncoordinated movements observed after SC dosing, were transient and were considered related to elevated cytokine concentrations and were consistent with other clinical findings, such as decreased activity and hunched posture (see toxicology section).

2.5.2.4. Pharmacodynamic drug interactions

No dedicated PD drug interaction studies were performed with epcoritamab. The potential interaction between epcoritamab and first-line therapy compounds (R-CHOP, i.e. R-CHOP- rituximab, cyclophosphamide, hydroxydaunorubicin, oncovin and prednisone), in case the patients who fail to respond to first-line therapies would still have these medicines present in the circulation, has been assessed as part of the primary pharmacology. It was determined that there was a low risk for pharmacodynamic interaction with first-line therapeutics of DLBCL.

2.5.3. Pharmacokinetics

The pharmacokinetics (PK) and toxicokinetics (TK) of epcoritamab were assessed as part of the exploratory, dose-range finding (DRF) and GLP single- and repeat-dose toxicology studies in cynomolgus monkeys with epcoritamab. Epcoritamab binds comparably to both, human and cynomolgus monkey CD3 and CD20, is pharmacologically active in cynomolgus monkey cells *in vitro*, and does not cross-react with rodent, pig, dog CD3 and CD20, thus confirming suitability of cynomolgus monkeys as the most reliable *in vivo* model for the *in vivo* toxicology studies, including PK/TK evaluations of epcoritamab. The studies were performed by the intravenous and subcutaneous route of administration and the latter is the intended clinical route of epcoritamab administration.

Method validation

Various analytical methods were developed and validated or qualified for detection of either epcoritamab or anti-epcoritamab antibodies in non-clinical studies. Initial non-GLP exploratory and dose-finding toxicology studies were supported by fit-for-purpose exploratory/qualified bioanalytical methods, while the bioanalytical methods supporting GLP-compliant toxicology study (Study No. 503484) were conducted in compliance with the OECD principles of GLP. The methods developed to measure epcoritamab and anti-epcoritamab antibodies in cynomolgus monkey plasma in the pivotal GLP toxicology study have been validated in accordance with relevant guidance documents (EMA/CHMP/ICH/172948/2019, EMEA/CHMP/114720/09, EMEA/CHMP/BMWP/14327/06). The single

molecule counting (SMC) method for detection of epcoritamab in cynomolgus monkey plasma was validated across a calibration range of 0.100 ng/ml to 50 ng/mL with an additional validated dilution factor of 1:2000, thus samples with a concentration up to 100 000 ng/mL in neat plasma could be quantified with this method. Incurred sample reanalysis (ISR) using SMC method was investigated in the GLP-compliant study (Study No. 503484). Overall ISR results were well within criteria (81.4% of the samples had the absolute relative difference ≤30.0%) which is in line with relevant guidance (EMA/CHMP/ICH/172948/2019) for ligand-binding assays. The stability of epcoritamab at QC levels in frozen matrix (-70°C) was demonstrated for up to 196 days. The maximum storage period between first blood sampling and last sample preparation was 189 days.

Levels of ADA in plasma samples of cynomolgus monkeys in the GLP 5-week toxicity study were assessed based on validated bridging ECLIA assay. The validated anti-epcoritamab bridging ECLIA assay had sensitivity of 31.9 ng/mL for CD20 and 78.1 ng/ml for CD3. Positive control CD20 was used in bioanalysis. In this assay it was possible to detect low positive control CD20 (100 ng/mL) in the presence of up to 15.6 mg/ml of epcoritamab. In the GLP pilot study (Study No. 503484), plasma concentrations of epcoritamab at the time of ADA determination were below this drug tolerance threshold.

Absorption

The pharmacokinetics in cynomolgus monkeys following subcutaneous administration of epcoritamab was described by dose-dependent kinetics, target-mediated drug elimination, delayed Tmax (3-7 days) and concentration dependent half-life of epcoritamab which is comparable to that observed in adult LBCL patients.

Single IV/SC dose

In the pivotal GLP toxicity study (Study No. 503484) in cynomolgus monkeys, the bioavailability of epcoritamab based on mean AUC(0-inf) was 85% and 49% in males and females, respectively, after single SC dose compared to single IV dosing at 1 mg/kg. At this dose, the peak plasma concentration was 10- to 17-fold lower after SC compared to IV dosing. The exposure AUC(0-t) was comparable after SC and IV. As expected, Tmax was delayed and occurred approximately 3 days in males and 3-7 days in females after SC-dosing compared to IV-dosing with Tmax 30 min after dosing. Following IV infusion, concentrations increased up to the end of the 30-minute dosing period and then decreased in a generally bi-phasic manner (Figure 3). After SC dosing, a more prolonged increase was observed up to a peak approximately 72 hours post dose and the concentration remained at a relatively steady level up to 168 hours and thereafter concentrations decreased in a mono-phasic manner up to the end of the 4-week sampling period (Figure 4). No consistent sex related differences in systemic exposure were noted following IV administration. However, exposure to epcoritamab was greater in males than females at 0.1 mg/kg and comparable at 1 and 10 mg/kg following SC administration.

Figure 1: Mean plasma concentrations (±SD) against time after a single IV dose of epcoritamab at 0.1 or 1 mg/kg

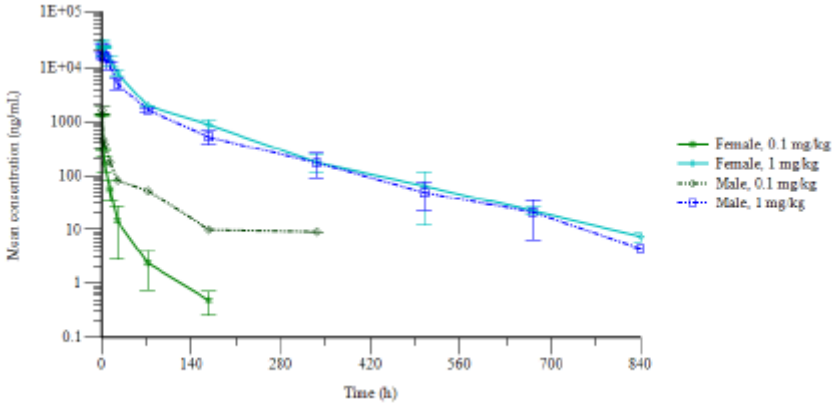
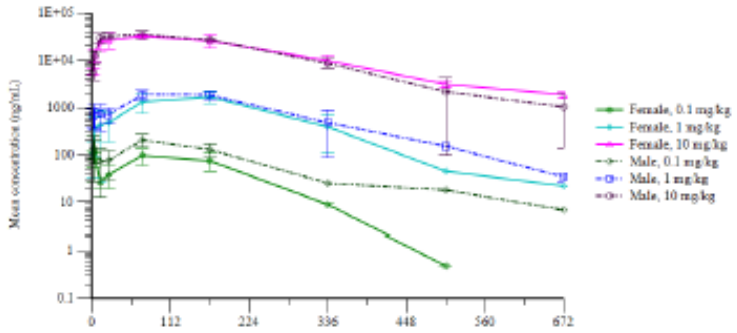


Figure 2: Mean plasma concentrations (±SD) against time after a single SC dose of epcoritamab at 0.1, 1, or 10 mg/kg



Epcoritamab displayed dose-dependent kinetics either following IV or SC single-dose administration to male and female cynomolgus monkeys. Systemic exposure to epcoritamab increased in a generally greater than dose-proportional manner between 0.1 and 1 mg/kg following IV administration, and between 0.1 and 10 mg/kg following SC administration, in both males and females. Accordingly, clearance appeared to decrease with higher dose as estimated in single dose study with IV administration of epcoritamab: clearance estimates were 518±442 ml/day/kg and 578±124 ml/day/kg in male and female animals dosed at 0.1 mg/kg, but 39.1±1.42 ml/day/kg and 29.0 ml/day/kg for male and female animals dosed at 1 mg/kg. These differences in clearance levels at different dose levels after IV administration could be attributed to differences in impact of target-mediated clearance and ADA-formation observed (i.e. higher ADA-formation and TMDD clearance at low dose (0.1 mg/kg)). Further, t1/2 of IV administered epcoritamab was estimated to be 2.0±1.1 days and 1.4±0.18 days for male and female animals when dosed at 0.1 mg/kg, and 4.1±1.1 days and 5.2 days for male and female animals when dosed at 1 mg/kg. Following SC single-dose administration to cynomolgus monkeys, t1/2 estimated to be 2.6±1.4 and 2.3±1.1 days in male and female animals at 1 mg/kg, and 4.3±2.7 and 6.0±1.0 days in male and female animals at 10 mg/kg dose. These data confirm a relatively long half-life of epcoritamab. Volume of distribution (Vss) was determined from IV single-dose study with epcoritamab and was estimated 1060±700 ml/kg and 1160±397 ml/kg in male and female animals dosed at 0.1 mg/kg, and 233±71.9 ml/kg and 226 ml/kg in male and female animals dosed at 1 mg/kg. Vss-values were greater than estimated plasma volume of cynomolgus monkeys, most likely due to specific binding of epcoritamab to its target cells (Table 15, Table 16).

Table 2: Mean TK parameters (±SD) for epcoritamab: single IV dose

Dose (mg/kg)	t_{max}[a, d] (day)	C_{max}[d] (µg/mL)	nC_{max}[d] (µg/mL)/ (mg/kg)	$AUC_{0\text{-}t}$[b, c, d] (µg·day/mL)	n$AUC_{0\text{-}t}$[b, c, d] (µg·day/mL)/(mg/kg)	$AUC_{0\text{-}inf}$[d] (µg·day/mL)	n$AUC_{0\text{-}inf}$[d] (µg·day/mL)/(mg/kg)	CL (mL/day/kg)	V_D (mL/kg)	V_{ss} (mL/kg)	$t_{½}$[d] (day)
0.1 (Males)	0.021	1.61 ± 0.252	16.1 ± 2.52	0.550 ± 0.700	5.50 ± 7.00	0.563 ± 0.721	5.63 ± 7.21	518 ± 442	1060 ± 700	198 ± 31.6	2.0 ± 1.1
0.1 (Females)	0.021	1.30 ± 0.0147	13.0 ± 0.147	0.177 ± 0.0366	1.77 ± 0.366	0.178 ± 0.0369	1.78 ± 0.369	578 ± 124	1160 ± 397	223 ± 34.8	1.4 ± 0.18
1 (Males)	0.021	21.6 ± 2.89	21.6 ± 2.89	25.5 ± 0.888	25.5 ± 0.888	25.6 ± 0.917	25.6 ± 0.917	39.1 ± 1.42	233 ± 71.9	109 ± 19.9	4.1 ± 1.1
1 (Females)[e]	0.021	28.4 ± 2.37	28.4 ± 2.37	26.5 ± 15.3	26.5 ± 15.3	35.0	35.0	29.0	226	80.1	5.2

[a] Median t_{max} reported.
[b] Male t_{last} was 168 or 336 hours (Days 8 or 15, respectively) at 0.1 mg/kg; 504 or 840 hours (Days 22 or 36, respectively) at 1 mg/kg.
[c] Female t_{last} was 168 hours (Day 8) at 0.1 mg/kg and 12.5 hours (6501) and 840 hours (Day 36) in all other females at 1 mg/kg.
[d] Units of amount of drug were adjusted to µg and units of time to days from ng and hours in the study report. Values for t_{max} and $t_{½}$ were rounded to two significant digits.
[e] Values presented for $AUC_{0\text{-}inf}$ through $t_{½}$ are mean values of two animals (6502 and 6503); standard deviation (SD) not calculated for n=2.

Table 3: Mean TK parameters for epcoritamab: single SC dose

Dose (mg/kg)	t_{max}[a, g] (day)	C_{max}[g] (µg/mL)	nC_{max}[g] (µg/mL)/ (mg/kg)	$AUC_{0\text{-}t}$[b, c, g] (µg·day/mL)	n$AUC_{0\text{-}t}$[b, c, g] (µg·day/mL)/ (mg/kg)	$AUC_{0\text{-}inf}$[g] (µg·day/mL)	n$AUC_{0\text{-}inf}$[g] (µg·day/mL)/ (mg/kg)	$t_{½}$[g] (day)	F[d, g] (%)
0.1 (Males)	3.0	0.244 ± 0.00416	2.44 ± 0.0416	1.54 ± 0.846	15.4 ± 8.46	2.01[f]	20.1[f]	3.6[f]	358[e]
0.1 (Females)	0.17	0.111 ± 0.0248	1.11 ± 0.248	0.671 ± 0.421	6.71 ± 4.21	1.14[f]	11.4[f]	1.8[f]	640[e]
1.0 (Males)	3.0	2.10 ± 0.112	2.10 ± 0.112	21.6 ± 4.75	21.6 ± 4.75	21.7 ± 4.79	21.7 ± 4.79	2.6 ± 1.4	85.0
1.0 (Females)	7.0	1.67 ± 0.449	1.67 ± 0.449	17.1 ± 6.88	17.1 ± 6.88	17.2 ± 7.00	17.2 ± 7.00	2.3 ± 1.1	49.0
10 (Males)	3.0	35.9 ± 5.68	3.59 ± 0.568	389 ± 17.8	38.9 ± 1.78	398 ± 25.3	39.8 ± 2.53	4.3 ± 2.7	-
10 (Females)	3.0	35.1 ± 0.805	3.51 ± 0.0805	385 ± 52.5	38.5 ± 5.25	401 ± 49.6	40.1 ± 4.96	6.0 ± 1.0	-

[a] Median t_{max} reported.
[b] Male t_{last} was 672 (7001), 336 (7002) or 168 (7003) hours (Days 29, 15, or 8, respectively) at 0.1 mg/kg; 504 or 672 hours (Days 22 or 29, respectively) at 1 mg/kg; and 672 hours (Day 29) at 10 mg/kg.
[c] Female t_{last} was 504 (7501) or 168 hours (7502 and 7503) (Days 22 or 8, respectively) at 0.1 mg/kg, 504 or 672 hours (Days 22 or 29, respectively) at 1 mg/kg and 672 hours (Day 29) at 10 mg/kg.
[d] Bioavailability (F) was calculated using $AUC_{0\text{-}inf}$.
[e] Value of F (%) is >100 indicating the terminal elimination phase was not appropriately identified leading to an appreciable underestimation of the AUC after IV dosing.
[f] Based on only two animals (males 7001 and 7002, 0.1 mg/kg) or one animal (female 7501, 0.1 mg/kg). SD not calculated for n=1 or 2; apparent terminal elimination phase not appropriately characterized in all animals.
[g] Units of amount of drug were adjusted to µg and units of time to days from ng and hours in the study report. Values for t_{max} and $t_{½}$ were rounded to two significant digits.

Repeat IV dose

The PK/TK evaluations in repeat dose study were performed only after intravenous administration of epcoritamab. In the pivotal 5-week GLP toxicity study (Study No. 503484: IV administration once weekly for 5 weeks at dose levels of 0.01, 0.1, or 1 mg/kg, n=6-10/group), ADA-formation was observed in all animals dosed at 0.01 and 0.1 mg/kg on Days 15 and 29 which greatly impacted plasma exposure, thus PK parameters could not be determined beyond the second dose. When animals were dosed at 1 mg/kg, ADA was detected in only 1 of 10 animals on day 15, and in 3 of 10 animals on day 22 and onward. At 1 mg/kg repeat IV dose, exposure was maintained for the duration of the study in the majority of animals and it was comparable between males and females. Systemic exposure to epcoritamab was greater after weekly dosing on days 15 and 29 compared to that after a single dose in males and females. A moderate accumulation of the drug was observed after multiple dosing resulting in day 29/day 1 accumulation ratios of 3.5 and 2.6 for males and females, respectively, which suggests less impact of target-mediated clearance over time. No significant change in Cmax was noted with repeat dosing; Days 15 and 29/Day 1 ratios of Cmax ranged from 1.0 to 1.5 (Table 17).

Table 4: Summary of epcoritamab TK parameters

Route	Day	Dose (mg/kg)	Parameter					
			C_{max}[a] (µg/mL)		AUC_{0-t}[a] (µg·day/mL)		AUC_{0-7d}[a] (µg·day/mL)	
			Male	Female	Male	Female	Male	Female
IV (infusion)	1	0.01	0.102	0.0957	0.00671	0.00596	0.00683	0.00608
		0.1	1.61	1.77	0.234	0.299	0.234	0.299
		1	24.0	24.6	23.9	27.0	23.9	27.0
	15	0.01[b]	-	-	-	-	-	-
		0.1[b]	-	-	-	-	-	-
		1	23.6	27.0	44.2	49.2	44.2	49.2
	29	0.01[b]	-	-	-	-	-	-
		0.1[b]	-	-	-	-	-	-
		1	37.2	28.5	100	82.5	84.2	71.3
Single IV (infusion)	1	0.1	1.61	1.30	0.550	0.177	-	-
		1	21.6	28.4	25.5	26.5	-	-
Single SC	1	0.1	0.244	0.111	1.54	0.671	-	-
		1	2.10	1.67	21.6	17.1	-	-
		10	35.9	35.1	389	385	-	-

[a]Units of amount of drug were adjusted to µg from ng in study report. Values were rounded to three significant digits.
[b]All animals dosed at 0.01 and 0.1 mg/kg on Days 15 and 29 exhibited a positive ADA response, therefore no TK parameters were reported.

ADA-formation and impact on non-clinical exposure parameters

Generally, across PK/TK studies in cynomolgus monkeys, ADA were formed following single- and repeat-dosing of epcoritamab which in some animals affected exposure, especially at doses ≤ 0.1 mg/kg following IV administration or at doses ≤ 1 mg/kg following s.c. administration. As such, it appeared that a dose of 1 mg/kg (IV) or higher (SC) was needed to prevent high frequency ADA development and thereby maintain drug exposure in long-term studies (up to 43 days). In the presence of ADA exposure levels of epcoritamab plasma concentrations from low dose groups (0.01 and 0.1 mg/mL) were appreciably low or non-quantifiable from day 15 or 22 onward, indicating faster clearance of test item due to ADAs. Therefore, animals which were ADA positive following repeat dosing were excluded from the PK/TK evaluation. Thus, ADA formation did not have impact on the interpretation of the PK data derived from 5-week IV repeat-dose toxicity study.

Distribution, metabolism, excretion

No distribution, metabolism or excretion studies were performed with epcoritamab. Specifically, IgG monoclonal antibody is expected to be degraded to small peptides and individual amino acids which are then used by the body or excreted in urine, and no urinary or renal excretion of monoclonal antibody is anticipated due to its molecular size.

Pharmacokinetic drug interactions

Non-clinical PK drug-drug interaction studies have not been conducted with epcoritamab. This is acceptable since catabolic pathways of mAb are not likely to be impacted by co-administered small-molecule medications. However, elevation of certain proinflammatory cytokines by epcoritamab may suppress CYP450 enzyme activities and should be taken into consideration

2.5.4. Toxicology

2.5.4.1. Single dose toxicity

In cynomolgus monkeys, single-dose IV and SC exploratory studies of epcoritamab were conducted to evaluate toxicokinetics (TK), tolerability, and reversibility of any potential toxicity. All findings following single dosing in the non-GLP studies in cynomolgus monkeys were reversible and were associated with the pharmacological action of epcoritamab, specifically related to acute phase reaction due to cytokine release and the depletion of lymphocyte B cell populations. All animals in the single dose studies developed ADA.

2.5.4.2. Repeat dose toxicity

The potential toxicity and toxicokinetics of epcoritamab when administered to cynomolgus monkeys by single (0.1, 1 mg/kg) or 5 weekly (0, 0.01, 0.1, 1 mg/kg) IV infusions or two monthly SC (0.1, 1.0, 10 mg/kg) injection was addressed in the pivotal GLP study (503484). Reversibility after 6 weeks recovery was evaluated at 1 mg/kg IV repeat dose.

In the non-GLP DRF study (501775), there were two unscheduled euthanasias in the SC dose groups. One female in the 1 mg/kg group had diarrhoea, dehydration, decreased lymphoid cellularity in thymus and spleen and was in poor general condition (sacrificed on Day 135). Second female in 20 mg/kg group had severe anaemia and was sacrificed on Day 57. Based on the findings, dose levels of 1 mg/kg IV and 10 mg/kg SC were chosen as high doses for repeated administration in the GLP study. Cytokine analyses indicated increases in TNF α, and IL-15 plasma concentrations, with dose-dependent increases in IL-2, IL-6, IL-8, IL-10, and IFN γ following either intravenous or subcutaneous administration. Cytokine release was observed at all dose levels, occurring primarily after the first dose, and returning to baseline levels within 24 hours postdose. Notably, IV administration of a priming dose (0.01 mg/kg) on Day 1 followed by a dose of 1 mg/kg on Day 2 was associated with much lower levels of cytokine release. Also, peak levels for most cytokines at a comparable dose were generally lower following SC administration relative to IV administration.

In the pivotal study, the IV administration of epcoritamab once weekly for 5 weeks at dose levels of 0.01, 0.1, or 1 mg/kg to cynomolgus monkeys was associated with changes in haematology and alterations in lymphocyte B-cell subpopulations at all dose levels. Overall, toxicity findings are consistent with T-cell activation and cytokine release, as well as findings secondary to cytokine release like clinical signs (decreased activity, hunched posture, emesis), acute phase reactions, and changes in leukocyte trafficking (activation and redistribution). Decreased lymphoid cellularity was recorded in the white pulp follicles of the spleen, lymph node follicles and GALT at ≥0.1 mg/kg. There was evidence of ongoing recovery of findings during the 6-week post dose observation period. One animal was euthanized at 1 mg/kg, due to poor general condition associated with elevated cytokines. A monthly SC administration of epcoritamab at dose levels of up to 10 mg/kg was well tolerated and associated with haematology changes and alterations in lymphocyte subpopulations observed at all dose levels. Decreased lymphoid cellularity was recorded in the white pulp follicles of the spleen, lymph node follicles and GALT at 1 or 10 mg/kg. There were no local injection reactions.

One female in 1 mg/kg IV dose group was euthanized 13 hours after a single dose. The symptoms (decreased activity, hunched posture, subdued and weak) were considered to be related to elevated cytokines and were regarded as an adverse reaction to the treatment. Vomiting, hunched posture and decreased activity were observed after the first IV and SC doses and generally resolved after 12-24 hours. After SC dosing, isolated cases of generalized reddened skin on the body surface were reported 4-12 hours post dose in males at all dose levels and females at 0.1 or 1 mg/kg. Slightly uncoordinated

movements were observed at 6 or 12 hours post dose in males at 0.1 or 10 mg/kg and in females at 1.0 or 10 mg/kg. No similar sign was observed in IV groups. These signs were not observed at dosing Day 29 and resolved without intervention after 12 hours.

Heart rate and RR, PR, QRS and QT intervals on Day 8 and 22 (repeated IV dosing) or Day 1 (single IV or SC dosing), and body weights were unaffected by treatment.

Single IV administration performed in the same pivotal repeat dose study, showed high total leukocyte, lymphocyte, monocyte, eosinophil, and basophil counts on Day 8 in males at 0.1 or 1 mg/kg. Similarly, high total leukocyte and lymphocyte counts on Days 15 and 22 in males and females at 0.1 or 1 mg/kg and eosinophil counts on Day 15 in males and females at 0.1 or 1 mg/kg. Counts were considered similar to pretreatment values on Days 29 and 36. Slightly lower haemoglobin concentrations and haematocrits were observed on Days 8 and 15 in males at 1 mg/kg.

There were no epcoritamab-related gross findings or organ weight changes. Histopathology evaluation identified decreased lymphoid cellularity observed in the spleen, lymph nodes and GALT. Both IV and SC routes of administration were well tolerated with no epcoritamab-related histopathological changes at the sites of administration.

The highest cytokine levels were observed after the first dose, and cytokine release was dose dependent. However, two individual animals' responses in the repeat intermediate dose group appeared to be different from the other group responses for several analytes (IL-12p40, IL-15, IL-1β, IL-4 and TNF-α), with cytokine release happening only after the second weekly dose. The reasons for that are unclear but might point to variations in cytokine release in monkeys.

Interspecies comparison

In the pivotal 5-week study (503484), the NOAEL in the IV repeat dosing group was 0.1 mg/kg, while the NOAEL in the SC dosing group was 10 mg/kg. At the highest IV dose of 1 mg/kg, the exposure in males and females was the same as the clinical AUC0-t at steady state. At the highest SC dose of 10 mg/kg, the exposure margins in males and females were 5x the clinical AUC0-t at steady state. At the highest IV dose of 1 mg/kg, the exposure margins in males and females were 8x to 6x the clinical Cmax at steady state, respectively. At the highest SC dose of 10 mg/kg, the exposure margins in males and females were 8x and 7x the clinical Cmax at steady state (see Table 18).

Table 5: Interspecies comparison - 5-week pivotal study

Route	Day	Dose (mg/kg)	Cmax (µg/mL)		AUC_{0-t} [a] (µg·day/ml)		AUC_{0-7d} (µg·day/ml)		$T_{1/2}$ (day)		Exposure multiple (AUC_{0-t})[c]		Exposure multiple (C_{max})[c]	
			M	F	M	F	M	F	M	F	M	F	M	F
Repeat IV	1	0.01	0.102	0.096	0.007	0.006	0.007	0.006	0.56	0.31	0.0	0.0	0.02	0.02
		0.1	1.61	1.77	0.234	0.299	0.234	0.299	1.2	1.4	0.0	0.0	0.34	0.37
		1	24.0	24.6	23.9	27.0	23.9	27.0	1.7	1.9	0.3	0.4	5.04	5.17
	15	0.01[b]	-	-	-	-	-	-	-	-	-	-	-	-
		0.1[b]	-	-	-	-	-	-	-	-	-	-	-	-
		1	23.6	27.0	44.2	49.2	44.2	49.2	1.9	2.4	0.6	0.7	4.96	5.67
	29	0.01[b]	-	-	-	-	-	-	-	-	-	-	-	-
		0.1[b]	-	-	-	-	-	-	-	-	-	-	-	-

		1	37.2	28.5	100	82.5	84.2	71.3	2.8	2.8	1.3	1.1	7.82	5.99
Single IV	1	0.1	1.61	1.30	0.550	0.177	-	-	2.0	1.4	0.0	0.0	0.34	0.27
		1	21.6	28.4	25.5	26.5	-	-	4.1	5.2	0.3	0.4	4.54	5.97
Single SC	1	0.1	0.244	0.111	1.54	0.671	-	-	3.6	1.8	0.0	0.0	0.05	0.02
		1	2.10	1.67	21.6	17.1	-	-	2.6	2.3	0.3	0.2	0.44	0.35
		10	35.9	35.1	389	385	-	-	4.3	6.0	5.2	5.2	7.54	7.37

2.5.4.3. Genotoxicity

In accordance with ICH S6 (R1) and ICH S9 guideline no information has been submitted on the genotoxic potential of epcoritamab.

2.5.4.4. Carcinogenicity

In accordance with ICH S6 (R1) and ICH S9 guideline no information has been submitted on the carcinogenic potential of epcoritamab.

2.5.4.5. Reproductive and developmental toxicity

Male and female fertility was investigated as part of the 5-week GLP study in sexually mature cynomolgus monkeys. There were no epcoritamab-related macroscopic or microscopic pathologic findings in the male or female reproductive organs. In line with the ICH S9 guideline, no dedicated studies investigating the effect of epcoritamab on fertility and early embryonic development (FEED) or pre- and postnatal toxicology (PPND) were performed. Human IgG1 antibodies are known to cross the placenta through binding to the FcRn. Animal studies with other agents targeting CD20 (rituximab, ofatumumab) have shown non-teratogenic effects on offspring (immunosuppression, perinatal death due to infections). Furthermore, cytokines are important for establishing and maintaining pregnancy in a stage-dependent fashion, therefore the CD3+ T-cell-dependent effects of epcoritamab may further contribute to foetal losses. Additionally, aberrant B-cell numbers and functions have been associated with obstetric complications, including growth restriction, pre-eclampsia and pregnancy induced hypertension. It can therefore be considered that epcoritamab has the potential to be transmitted from the pregnant mother to the developing foetus, and that foetal exposure to epcoritamab may cause adverse developmental outcomes, such as B-cell lymphocytopenia and alterations in normal immune responses in infants exposed in utero. Based on the above information, an EFD study can be waived.

It is not known whether or to what extent epcoritamab is excreted in human milk. Because IgGs are known to be present in milk prevailingly during the first few days after birth and can be transferred to neonates in this time period, it is also likely that neonatal exposure to epcoritamab may occur via lactational transfer only in the first few days after birth. However, due to the long half-life of epcoritamab and potential local GI tract effects in the suckling child, a waiting period of 4 months is justified.

2.5.4.6. Toxicokinetic data

Toxicokinetic data collected during the pivotal toxicity study is described in the section on Pharmacokinetics.

2.5.4.7. Local Tolerance

Local tolerance was evaluated as part of the single or repeat dose studies following IV or SC administration in cynomolgus monkeys. No changes were observed that would indicate local intolerance.

2.5.4.8. Other toxicity studies

The potential for generation of antibodies to epcoritamab was assessed in the single- and repeat-dose studies, and epcoritamab had high potential for immunogenicity in cynomolgus monkeys. However, in the pivotal study, only few animals in the high IV and SC dose groups (1 mg/kg IV; 10 mg/kg SC) developed ADA by the end of the study. In these dose groups, high exposures were maintained in most animals until Day 29.

In the cytokine release assay, the cytokines released with the clearest trend in concentration-response included IL-2, IL-6, IL-8, IL-10, IFNγ, and TNFα.

Epcoritamab was non-haemolytic in a human whole blood assay in vitro at concentrations of 1.0 µg/mL and 20 µg/mL. No red blood cell clumping or plasma precipitation was observed in human whole blood at the concentrations tested.

Tissue cross-reactivity (TCR) studies were conducted to evaluate the potential cross-reactivity of epcoritamab with a comprehensive panel of normal human and cynomolgus monkey tissues. Epcoritimab was shown to bind specifically to mononuclear cells (B/T lymphocytes) in human and cynomolgus monkey lymphoid tissues.

2.5.5. Ecotoxicity/environmental risk assessment

Monoclonal antibodies are expected to be readily biodegradable and of low ecotoxicity. The active substance is a monoclonal antibody, the use of which will not alter the concentration or distribution of the substance in the environment. Based on these considerations, epcoritamab is not expected to pose a risk to the environment.

2.5.6. Discussion on non-clinical aspects

Epcoritamab is a bispecific antibody recognising the T-cell antigen CD3 and the B-cell antigen CD20. Epcoritamab has a regular IgG1 structure and biochemical characteristics typical of a human IgG1antibody. It has been developed as an anti-cancer therapeutic agent for the treatment of a diffuse large B-cell lymphoma (DLBCL), expressing CD20.

The pharmacology of epcoritamab has been thoroughly described in the provided non-clinical package. The nonclinical studies have been conducted in accordance with EMA and international (ICH) regulatory guidelines. Non-clinical pharmacology studies and initial toxicology studies have been performed with research grade batches representative of the material used in the clinical trials, while pivotal GLP toxicology study has been performed by clinical grade batch. The batches behaved similar with respect to pharmacological activity.

A preclinical data demonstrated the potency and mechanism of epcoritamab in *in vitro* and *ex vivo* studies using human cells and tissues, as well as in *in vivo* studies using three different human cell-derived xenograft models or patient derived xenograft model in different types of humanised mice. Non-clinical tumour models used in the non-clinical pharmacology program are representative of Non-Hodgkin lymphomas, including target indication DLBCL. Epcoritamab showed potent killing of CD20-

positive cells by both CD4+ and CD8+ T cells *in vitro* and *in vivo*. Concentrations at which T-cell activation and cytotoxicity by epcoritamab were first observed (EC20) were in the very low pM range and those at which half-maximal T-cell activation and cytotoxicity were observed (EC50) were in the low pM range. Activation and cytotoxicity of T cells induced by epcoritamab were dependent on the simultaneous binding of Fab arms to both CD3-positive T cells and CD20-positive B cells or tumour cells. While EC50 values for T-cell activation and T-cell mediated cytotoxicity in cell lines were in the pM range, the EC50 values for binding to CD20 were in the nM range. This indicates that low target occupancy is sufficient to achieve substantial cytotoxicity. This is further supported by lack of correlation between EC50 for activation and cytotoxicity and expression levels of CD20 per cell in tumour cell lines, and more than 40% tumour cell kill in patient samples even when the last anti-CD20 treatment had been administered only two weeks prior to sampling, suggesting that epcoritamab can have pharmacodynamic effects shortly after discontinuing treatment with a CD20 mAb.

For three DLBCL cell lines in study report GMB3013-032, however, the EC50 values for cytotoxicity was high although the EC50 for T-cell activation was rather low. And in two DLBCL samples from newly diagnosed patients no epcoritamab-induced cytotoxicity was observed (study report GMB3013-072). It is suggested by the applicant that there may be some characteristics other than T-activation or CD20 expression that makes them less sensitive, and exploratory biomarkers will be evaluated as part of the expansion phase in clinical study GCT3013-01.

Fc domain was silenced by introduction of mutations L234F L235E D265A which resulted in inability of epcoritamab to bind human receptor subtypes FcγRI, FcγRIIb, FcγRIIa-131H/R and FcγRIIIa-158F/V to elicit effector functions. However, receptor subtypes FcγRIIc (expressed on NK cells) and FcγRIIIb (expressed on neutrophils and eosinophils) have not been evaluated. The applicant justified the omission of these data by identical or very similar extracellular domains of FcγRIIb vs. FcγRIIc and FcγRIIIa vs. FcγRIIIb receptors, considering Fc interacting region. Thus, binding data generated for FcγRIIb and FcγRIIIa are applicable for FcγRIIc and FcγRIIIb. Epcoritamab showed minimal C1q binding and reduced capacity to induce CDC in CD20-positive cells at clinically relevant concentrations (7 % relative to IgG1-CD20). Based on the applicant´s explanation, it is reasonable to assume that observed minimal CDC activity of epcoritamab is not expected to have significant impact on clinical AEs. The proposed text in SmPC- section 5.1 with regard to MoA, is supported.

The potential interaction between epcoritamab and first-line therapy compounds (R-CHOP, i.e R-CHOP-rituximab, cyclophosphamide, hydroxydaunorubicin, oncovin and prednisone), has been assessed as part of *in vitro*, *ex vivo* and *in vivo* pharmacology studies. It was demonstrated that there is a low risk for pharmacodynamic interaction of epcoritamab in the experimental set-up of the study with first-line therapeutics of DLBCL.

The immunogenicity of humanized CD3-specific Fab arm and the Fc region of epcoritamab has been evaluated by *in silico* and *in vitro* cell-based modelling approaches and the immunogenic potential in human was predicted to be low which is line with clinical observations.

In vivo, using B-cell lymphoma cell-derived xenograft models (CDX) or DLBCL patient-derived xenograft (PDX) model in mice with or with human immune system (HIS), epcoritamab delayed the growth of CD20+ tumour in all tested mouse models. Epcoritamab delayed the growth of CD20+ tumour in presence of T-cells, whereas bsAb-CD3xctrl which lacks the CD20-specific arm, did not. Interestingly, bsAb-ctrlxCD20 that lacks the CD3-specific arm, induced some anti-tumour activity and peripheral blood human B-cell depletion in Raji-luc xenograft model using BRGS-HIS mice, however, this treatment did not significantly prolong survival of the mice compared to PBS group. In Burkitt's lymphoma CDX model (Raji cells) using NSG mice with HIS, low doses (0.05 mg/kg and 0.5 mg/kg) appear to have a delayed but strong effect, whereas high dose (5 mg/kg) has an immediate but less strong effect. As suggested by the applicant, the effect observed is primarily due to the model used,

having limited number of available CD3 expressing T-cells, which consequently could limit dose-dependent effect. Explanation that this phenomenon is restricted specifically to this preclinical model and the observation with the stronger anti-tumor effects at a lower dose is not clinically translatable, can be followed. In HIS mice that were implanted SC human tumour biopsy material (DLBCL patient-derived xenograft model), epcoritamab effectively delayed tumour growth only at the highest tested dose (5 mg/kg) which was reflected in prolonged progression-free survival. However, efficacy appears to be transient, as tumour volume increases before the last dose is given.

To identify a relevant non-human species to assess the nonclinical safety of epcoritamab, cross-reactivity of epcoritamab was evaluated with CD20 and CD3 of non-human origin. The cynomolgus monkey was the only evaluated non-human species, for which binding of epcoritamab to both CD3 and CD20 was highly comparable with its binding to human CD3 and CD20. Moreover, CD3 and CD20 expression levels were comparable between human and cynomolgus monkey cells and epcoritamab showed comparable pharmacology in human and cynomolgus monkey PBMCs. As part of toxicology studies, pharmacologic effects including cytokine release, depletion of peripheral blood B cells and decreased lymphoid cellularity in lymphoid tissues were observed by IV and SC administered epcoritamab in cynomolgus monkeys with normal B-cells.

The bioanalytical methods were developed and validated or qualified for detection of either epcoritamab or anti-epcoritamab antibodies in plasma sample of cynomolgus monkeys. Initial non-GLP exploratory and dose-finding toxicology studies were supported by fit-for-purpose exploratory/qualified bioanalytical methods, while the bioanalytical methods supporting GLP-compliant toxicology study (Study No. 503484) were conducted in compliance with the OECD principles of GLP. The single molecule counting (SMC) method for detection of epcoritamab in cynomolgus monkey plasma from pilot GLP toxicity study was validated according to the relevant guideline on Bioanalytical method validation and study sample analysis for ligand binding assays (EMA/CHMP/ICH/172948/2019). The missing validation report of long-term stability for epcoritamab in frozen cynomolgus monkey plasma samples (-70°C) has been submitted upon request. The stability results of sample storage up to 196 days are acceptable.

Overall, the pharmacokinetics of IV administered epcoritamab in cynomolgus monkeys showed a target-mediated drug disposition. A super-proportional increase in exposure was observed with increased IV and SC dose, as well as accumulation with weekly IV dosing. The SC profile in comparison to IV administration showed lower Cmax (10-17-fold), longer Tmax (3-7 days), shorter T1/2 (1.6-2.3-fold), and 50-85% bioavailability. The applicant has confirmed that the apparent discrepancies in T1/2 values in the submitted dossier was due to an incorrect statement in the study report.

In female monkeys, a substantial range of bioavailability was observed between studies. Following single SC doses of 1 mg/kg, bioavailability ranged from more than 100% in females in the dose range-finding toxicity study to approximately 49% in the pivotal toxicity study. The applicant informed that in the DRF study bioavailability was calculated using values from different groups (single SC dose and QW repeated IV dose), whereas in the GLP toxicity study both routes of administration had a dedicated single dose arm. Overall, it is agreed that the exposure data and sample size varied between toxicology studies and therefore the comparison of the results from different studies is challenging. Moreover, in the pivotal GLP toxicology study SC bioavailability differed between female (49%) and male cynomolgus monkeys (85%), consistent with the different median Tmax values at 1 mg/kg dose (up to 7 days in females and 3 days in males). The applicant explained that observed differences in bioavailability between males and females could partly be attributed to ADA formation towards the later time points in the TK profiles. In addition, variable number of females were included in IV and SC dose groups affecting the calculations of the group average AUC0-inf which may introduce bias between sexes. Taken together, there is no reason to assume significant gender differences in bioavailability.

No dedicated PD drug interaction studies were performed with epcoritamab according to CPMP/EWP/560/95/Rev.1. This is acceptable because epcoritamab showed high binding specificity toward human CD20-expressing B-cells and CD3-expressing T-cells.

No distribution, metabolism or excretion studies were performed with epcoritamab. This is acceptable according to ICHS6(R1) since no tissue distribution studies are considered necessary as epcoritamab is expected to be metabolised and excreted in the same manner as endogenous antibodies.

ADA responses occurred in animals from D15 treated IV or SC. ADA were formed following single- and repeat-dosing of epcoritamab which in some animals affected exposure to significantly low or non-quantifiable levels, especially at doses ≤ 0.1 mg/kg following IV administration or at doses ≤ 1 mg/kg following s.c administration. ADA had significant effect on exposure levels in these animals, therefore, animals which were ADA positive following repeat dosing were excluded from the PK/TK evaluation. Thus, ADA formation did not have impact on the interpretation of the PK data derived from IV repeat-dose toxicity study.

The nonclinical safety assessment of epcoritamab consisted of *in vitro* studies in human cells and tissues (cytokine release assay, plasma compatibility assays and tissue cross reactivity evaluation), and *in vivo* toxicology studies in cynomolgus monkeys. Repeat dose toxicology studies with once weekly IV administration up to five weeks duration, as well as single dose SC and monthly (two doses a month apart) SC administration have been conducted in the cynomolgus monkey. The proposed regimen for humans, with priming and intermediate dose, was not addressed in monkeys, however a regimen with priming dose followed by a full dose was used in the DRF monkey study, which is deemed sufficient.

Only short-term studies of up to 5 weeks for repeated dosing of epcoritamab were performed. Since no unexpected findings were observed with epcoritamab in the repeat-dose toxicity studies and since a large proportion of animals developed ADA following repeat IV dosing, a 13-week toxicity study would be of limited value for the safety of epcoritamab, and can be waived.

The primary findings in the repeat dose toxicology studies included adverse clinical signs, such as vomiting, skin reddening and mortality at ≥ 1 mg/kg after the first dose. These findings were associated with elevated cytokines. Additional epcoritamab findings included reversible changes in leukocytes and lymphocytes, reversible B-cell depletion in peripheral blood and reversible decrease in lymphoid cellularity in lymphoid tissues (spleen, various lymph nodes, and GALT), all of which were considered related to the pharmacological activity of epcoritamab. Slightly lower haemoglobin concentrations and haematocrits were also observed. There were no local injection reactions after SC administration. The potential for generation of antibodies to epcoritamab was assessed in single- and repeat-dose studies, and across all doses and routes. Epcoritamab had high potential for immunogenicity in cynomolgus monkeys.

Due to the mode of action of epcoritamab and the evolutionary proximity to humans, doses used in the pivotal study were not much higher than the clinical dose. At the highest IV dose of 1 mg/kg, the exposure in males and females was the same as the clinical AUC0-t at steady state. At the highest SC dose of 1mg/kg, the exposure margins in males and females were 5x the clinical AUC0-t at steady state. At the highest IV dose of 1 mg/kg, the exposure margins in males and females were 8x to 6x the clinical Cmax at steady state, respectively. At the highest SC dose of 10 mg/kg, the exposure margins in males and females were 8x and 7x the clinical Cmax at steady state.

The findings in cynomolgus monkeys were well described and correlated with the identified risk of cytokine release syndrome in humans. Information on cytokine release has been included in the SmPC. Cytokine release in monkeys was dose dependent and usually the highest after the first dose. SC administration resulted in lower cytokine levels than IV administration of equivalent dose. In the non-

GLP study in monkeys, a regimen of priming and single full dose on the subsequent day elicited a lower cytokine release than the regimen with repeat full dose of 1 mg/kg.

Although non-clinical data does not directly support the proposed dosing regimen in humans, the toxicology data indicate that the highest levels of cytokines were associated with the first epcoritamab application and with the higher doses. Therefore, the severe cytokine release can be avoided with the use of a low starting, followed by intermediate dose (see Clinical part).

In accordance with ICH S6 (R1) and ICH S9 guideline no information has been submitted on the genotoxic or carcinogenic potential of epcoritamab.

Reproductive toxicity studies have not been conducted for epcoritamab due to the high potential for immunogenicity in cynomolgus monkeys as well as limited tolerability due to its mode of action. The applicant has presented an adequate literature review to justify the absence of EFD toxicity study. Animal studies with other agents targeting CD20 (rituximab, ofatumumab) have shown non-teratogenic effects on offspring (immunosuppression, perinatal death due to infections). Furthermore, cytokines are important for establishing and maintaining pregnancy in a stage-dependent fashion, therefore the CD3+ T-cell-dependent effects of epcoritamab may further contribute to foetal losses. Additionally, aberrant B-cell numbers and functions have been associated with obstetric complications, including growth restriction, pre-eclampsia and pregnancy induced hypertension. It can therefore be considered that epcoritamab has the potential to be transmitted from the pregnant mother to the developing foetus, and that foetal exposure to epcoritamab may cause adverse developmental outcomes. This information is included in the SmPC. The waiting period after dosing recommended for pregnancy is considered adequate.

It is not known whether or to what extent epcoritamab is excreted in human milk, but based on the available data, local GI tract adverse effects cannot be ruled out, and a waiting time of 4 months -as recommended under section 4.6 of the SmPC- is justified.

The results of the *in vitro* cytokine release assay were consistent with the anticipated pharmacology of epcoritamab, as well as findings in cynomolgus monkeys administered epcoritamab. They confirm the well-characterised risk of cytokine release associated with T cell activation in immunotherapy. Epcoritamab was non-haemolytic in a human whole blood assay in vitro and no plasma precipitation was observed in human whole blood at the concentrations tested. In the tissue cross-reactivity testing (TCR), epcoritamab was shown to bind specifically to mononuclear cells in human and cynomolgus monkey lymphoid tissues. The staining pattern of epcoritamab in the TCR studies was consistent with the expected tissue distribution of B/T lymphocytes in normal human and cynomolgus monkey tissues.

The proof of concept for epcoritamab is considered sufficiently demonstrated. Epcoritamab was shown to be cross reactive with both, CD20 and CD3, only in human and cynomolgus monkeys, which support the use of cynomolgus monkey as an in vivo model in PK/TK and toxicity studies. Pharmacologic effects observed in cynomolgus monkeys are consistent with the mode of action of epcoritamab. Pharmacokinetic/toxicokinetic profile of epcoritamab is well described. Effects of epcoritamab observed in cynomolgus monkeys included cytokine release and consequent clinical signs (vomiting, hunched posture, subdued behaviour), depletion of peripheral blood B cells, and decreased lymphoid cellularity in lymphoid tissues (spleen, various lymph nodes, and GALT) and lower haemoglobin concentrations and haematocrit. The findings considered associated with elevated cytokine levels were observed primarily following the first and the high dose.

The active substance is a monoclonal antibody and as such it can be considered in the same way as a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, epcoritamab is not expected to pose a risk to the environment.

2.5.7. Conclusion on the non-clinical aspects

An adequate in vitro, ex-vivo and in vivo pharmacology studies were conducted for epcoritamab, including target disease models which supports the intended clinical use of epcoritamab.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Union were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Tabular overview of clinical studies

Table 6: Clinical studies used to support epcoritamab application

Trial Phase	Trial Population	Epcoritamab Doses	PK Sampling Times	No. of Subjects Treated/No. of PK-Evaluable Subjects[a]
GCT3013-01 (Global) Phase 1/2	Adult subjects with relapsed, progressive, and/or refractory mature B-cell lymphoma who had received an anti-CD20 monoclonal antibody potentially in combination with chemotherapy and/or relapsed after autologous stem cell rescue	Dose Escalation Part: Titrated dose levels • Priming: 0.004, 0.0128, 0.04, 0.08, 0.12, and 0.16 mg • Intermediate: 0.25, 0.5, 0.8, or 1.6 mg • Full: 0.0128, 0.04, 0.12, 0.38, 0.76, 1.5, 3, 6, 12, 24, 48, and 60 mg	• At predose, 1, 6 hours (after dose), 1, 2, and 3 days during 1st and 2nd dose in Cycle 1 • At predose, 1, 6 hours (after dose), 1 and 2 days during 3rd and 4th dose in Cycle 1 • At predose during 1st, 2nd, 3rd, and 4th dose in Cycle 2 • At 4 days (after dose) during 1st and 2nd dose in Cycle 2 • At predose during 1st and 3rd dose in Cycles 3-6 • At predose during 1st dose in Cycle 7 and onward	Treated: 68 PK-evaluable: 35
		Dose Expansion Part: • Priming dose: 0.16 mg • Intermediate dose: 0.8 mg • Full dose: 48 mg	• At predose during 1st, 2nd, and 4th dose in Cycle 1 • At predose, 1 hour (after dose), and 1 day during 3rd dose in Cycle 1 • At predose and 1 hour (after dose) during 1st, 2nd, and 3rd dose in Cycles 2-3 • At predose and 1 hour (after dose) during 1st and 3rd dose in Cycles 4-9 • At predose and 1 hour (after dose) during 1st dose in Cycle 10 and onward	Treated: 299 total (157 aNHL, 105 iNHL, 37 MCL) PK-evaluable: 145 aNHL (DLBCL) 71 iNHL 16 MCL
GCT3013-04 (Japan) Phase 1/2	Adult Japanese subjects with relapsed or refractory mature B-cell non-Hodgkin lymphoma who had received at least 2 prior systemic therapies	Dose escalation (Part 1): Step up dosing • Priming dose: 0.16 mg • Intermediate dose: 0.8 mg • Full dose: 48 mg	• Predose after 1st dose in Cycle 1 • At predose, 1 hour (after dose), 2, 3, and 4 days during 2nd and 3rd dose in Cycle 1 • At predose, 1, 6 hours (after dose), 2 and 5 days after 4th dose in Cycle 1 • At predose after 1st, 2nd, 3rd, and 4th dose in Cycles 2-3 • At predose after 1st and 3rd dose in Cycles 4-9 • At predose after 1st dose in Cycle 10 on onward	Treated: 9 PK-evaluable: 9
		Expansion (Part 2): Step-up dosing • Priming dose: 0.16 mg • Intermediate dose: 0.8 mg • Full dose: 48 mg	• Predose after 1st dose in Cycle 1 • At predose, and 1 hour (after dose), 2nd, 3rd, and 4th dose in Cycle 1 • At predose after 1st, 2nd, 3rd, and 4th dose in Cycles 2-3 • At predose after 1st and 3rd dose in Cycles 4-9 • At predose after 1st dose in Cycle 10 on onward	Treated: 57 total (36 DLBCL 21 FL) PK-evaluable: 33 DLBCL 15 FL

Abbreviations: aNHL = aggressive B-cell non-Hodgkin lymphoma; DLBCL = diffuse large B-cell lymphoma; FL = follicular lymphoma; iNHL = indolent non-Hodgkin lymphoma; MCL = mantle cell lymphoma; PK = pharmacokinetic(s).
a. PK evaluable as defined in trial statistical analysis plan and CSR
Data cutoff date: 30 Nov 2021 for pharmacokinetics and immunogenicity data and 31 Jan 2022 for other data

Epcoritamab is available at two strengths 5 mg/mL concentrate for injection and 60 mg/mL solution for injection, which are intended for administration of priming/intermediate and full doses, respectively. Epcoritamab is administered by SC injection in treatment cycles of 28 days. The proposed dosing regimen includes an initial priming dose of 0.16 mg on C1D1, an intermediate

dose of 0.8 mg on C1D8, and a full dose of 48 mg on C1D15, C1D22, and thereafter, administered according to the following schedule:

- Cycles 1 to 3: QW on Days 1, 8, 15, and 22
- Cycles 4 to 9: Q2W on Days 1 and 15
- Cycles 10 and beyond until unacceptable toxicity or PD: Q4W on Day 1

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

Clinical pharmacology data are available from two ongoing clinical trials (Table 19) to support the use of epcoritamab monotherapy in LBCL and DLBCL: global phase 1/2 trial GCT3013-01 (Dose Escalation and Expansion LBCL, iNHL, and MCL cohorts) and supportive Japanese phase 1/2 trial GCT3013-04 (Dose Escalation, Expansion DLBCL and FL cohorts). The epcoritamab clinical pharmacology program included the evaluation of single dose PK, multiple dose PK, effects of relevant intrinsic and extrinsic covariates on epcoritamab exposure evaluated by a popPK approach, QT prolongation potential, immunogenicity, B cell/T cell counts, and cytokine release. Pharmacology of epcoritamab has not been evaluated in healthy subjects, only in cancer patients.

Methods

Bioanalytical methods. To quantify epcoritamab in human plasma for PK evaluation, two bioanalytical assays were used. SMCIA-139 method was a sandwich immunoassay with fluorescence detection (60 pg/mL-500 pg/mL) developed and validated for samples with expected low concentrations from the Escalation Part of GCT3013-01. The ECLIA-139 sandwich immunoassay with electrochemiluminescence detection (10.0 ng/mL and the ULOQ at 1,000 ng/mL) was used for the vast majority of the PK samples (88.7%) from the GCT3013-01 and GCT3013-04 studies. Because cross-validation showed that the two methods do not sufficiently produce comparable results in the overlapping assay range, only data with the ECLIA-139 method were reported.

Immunogenicity assessment of anti epcoritamab antibodies (ADA) in plasma (study GCT3013-01) or serum (GCT3013-04) was evaluated following a tiered approach that included screening, confirmation, and titer analysis. In study GCT3013-04, in addition a domain binding method was also applied to determine the ADA titers for the separate arms of epcoritamab. No neutralising ADA assay was submitted.

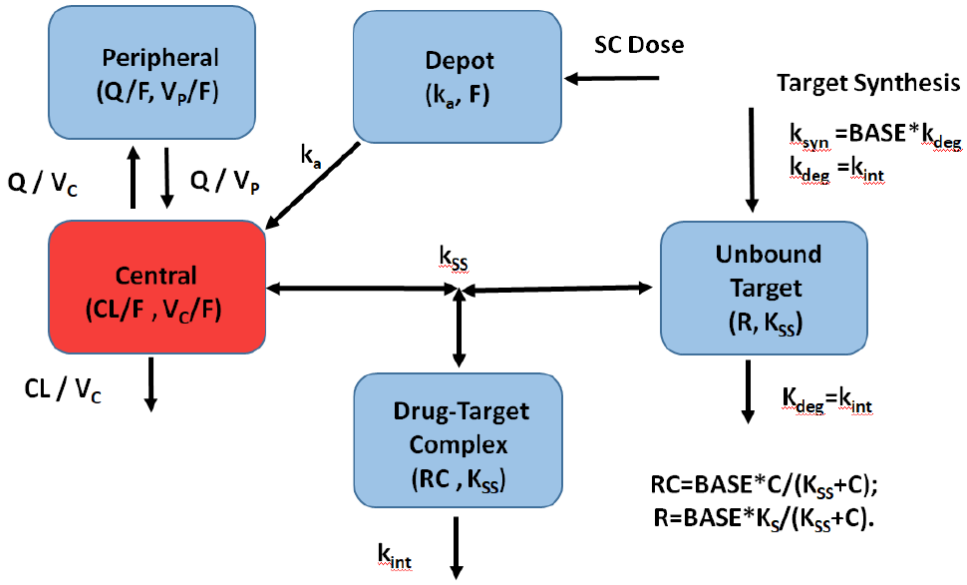
PopPK analysis. PopPK analysis was used to characterise the pharmacokinetics, to assess the impact of covariates on the PK of epcoritamab and to estimate individual post hoc pharmacokinetic parameters for use in exposure-response analysis. The data cut-off date was 30-Nov-2021 for PK and 31-Jan-2022 for the clinical data.

The PopPK analysis was based on 6819 quantifiable PK samples from 327 subjects (including 300 subjects who were administered the full dose of 48 mg). The analysis was conducted using nonlinear mixed-effects modelling with the NONMEM software, Version 7.5.0 (ICON Development Solutions). FOCEI was used for NONMEM model runs of the primary analysis and LAPLACIAN estimation method was used for sensitivity analysis. 953 postdose concentrations that were below the limit of quantification (BLQ) were included in a BQL sensitivity analysis; 87.7% of BQL observations followed priming, intermediate, or full doses that were below 1 mg. The likelihood-based M3 method for handling BQL data was used. Furthermore, 921 quantifiable samples analysed by SMCIA were included

in another sensitive analysis. 392 postdose observations that were analysed outside of stability window, all from study GCT3013-01 dose escalating part, were not included in the popPK analysis.

Pharmacokinetics of epcoritamab was described by a 2-compartment model with a non-specific linear clearance and a target mediated drug clearance (TMDD, a QSS approximation) with the first order SC absorption (Figure 5).

Figure 3: Schematics of the base population PK model



Abbreviations: K_a = absorption rate constant; K_{int} = elimination rate constant of the drug-target complex; K_{ss} = QSS constant; PK = pharmacokinetics; Q/F = apparent inter-compartmental clearance; SC = subcutaneous; Vc/F = apparent central volume of distribution; Vp/F = apparent volume of distribution in the peripheral compartment.

Model development, performance evaluation and reporting of the popPK model was good and in line with the guideline. Pharmacokinetics of epcoritamab was described by a 2-compartment model with a non-specific linear clearance and a target mediated drug clearance (TMDD, a QSS approximation) with the first order SC absorption (Figure 5). The model described the pharmacokinetics of epcoritamab dosed 48 mg sufficiently well.

Only body-weight (CL/F, Vc/F) and age (ka) were covariates for the non-specific linear clearance, distribution and absorption of epcoritamab. After adjusting for body-weight and age effects, Asian race, sex, tumour size, ALB, trial effect (04 vs. 01), lymphoma subtypes (iNHL vs. LBCL and MCL vs. LBCL) did not have significant impact on the PK of epcoritamab. Parameter estimates of the final popPK model are given in Table 20. Base model CV% for CL and Vc were 34.6% and 39.6%, respectively.

Table 7: Parameter estimates of final popPK Model (run 154) (popPK report)

Parameter		Description	Value	RSE%	95% CI
CL/F (L/day)	θ_1	Apparent nonspecific clearance	0.481	2.66	0.456; 0.506
Q/F (L/day)	θ_2	Apparent inter-compartment clearance	0.488	7.88	0.413; 0.563
V_C/F (L)	θ_3	Apparent central volume	9.33	3.18	8.75; 9.91
V_P/F (L)	θ_4	Apparent peripheral volume	14.1	10.9	11; 17.1
k_a (1/day)	θ_5	Absorption rate constant	0.584	4.94	0.527; 0.64
BASE (µg/mL)	θ_6	Total target concentration	2.03	5.84	1.8; 2.26
K_{SS} (µg/mL)	θ_7	Quasi-steady-state constant	0.214	7.27	0.183; 0.244
k_{int} (1/day)	θ_8	Drug-target complex elimination rate	0.0278	9.31	0.0227; 0.0328
σ_{prop}	θ_9	Residual error: proportional part (CV)	0.189	1.64	0.183; 0.195
σ_{add} (µg/mL)	θ_{10}	Residual error: additive part (SD)	0.0133	3.01	0.0125; 0.0141
CL_{WT}	θ_{13}	Weight effect on CL/F	0.875	10.7	0.692; 1.06
Q_{WT}	θ_{14}	Weight effect on Q/F	0.75	Fixed	
$V_{C,WT}$	θ_{15}	Weight effect on V_C/F	0.603	16.6	0.407; 0.8
$V_{P,WT}$	θ_{16}	Weight effect on V_P/F	1	Fixed	
$k_{a,age}$	θ_{17}	Age effect on k_a	-0.503	33	-0.827; -0.178

Parameter		Value	RSE%	95% CI	CV	Shrinkage
ω^2_{CL}	Ω_{11}	0.0659	12.2	0.0501; 0.0817	CV=25.7%	34.2%
ω^2_{Q}	Ω_{22}	0.756	14.2	0.546; 0.967	CV=87%	30.0%
ω^2_{VC}	Ω_{33}	0.097	14.1	0.0703; 0.124	CV=31.2%	26.3%
ω^2_{VP}	Ω_{44}	1.89	14.3	1.36; 2.42	CV=137.5%	21.6%
ω^2_{ka}	Ω_{55}	0.299	9.25	0.245; 0.353	CV=54.7%	23.6%
ω^2_{BASE}	Ω_{66}	0.39	12.7	0.293; 0.487	CV=62.4%	25.2%
ω^2_{KSS}	Ω_{77}	0.718	13.3	0.531; 0.904	CV=84.7%	28.7%
ω^2_{kint}	Ω_{88}	0.57	20.3	0.344; 0.797	CV=75.5%	43.1%
$\omega^2_{\sigma 1}$	Ω_{99}	0.0448	10.7	0.0353; 0.0542	CV=21.2%	7.8%
σ^2	Σ_{11}	1	fixed			4.1%

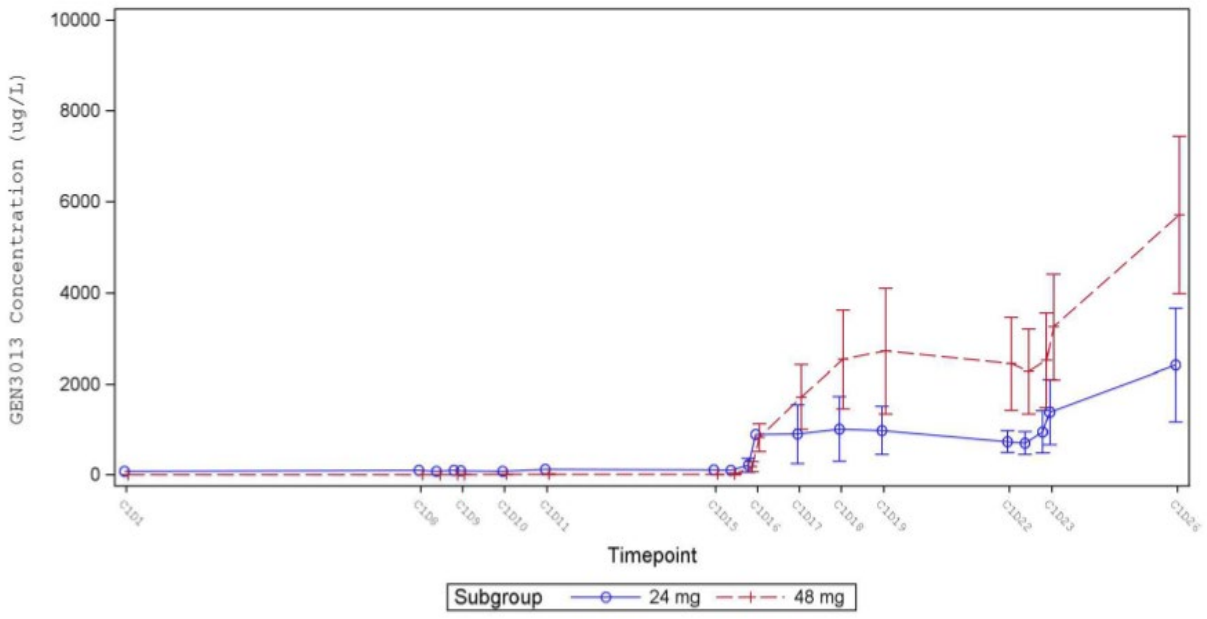
Abbreviations: 95% CI = 95% confidence interval; CV = coefficient of variation; NONMEM = Nonlinear Mixed-Effect Modeling software; RSE% = relative standard error = 100·abs(SE/PE); SE = standard error.
The NONMEM combined control and output file of Model 154 can be found in Appendix 11.2.2. The observed concentrations overlaid with the individual and population predictions for each subject can be found in Appendix 11.3.
Source: 154ParEst.csv (DiagnosticPlots.R)

Parameters are given for a typical patient with body weight 75 kg and age 65 years.

Absorption

Epcoritamab has been administered only subcutaneously. Absolute bioavailability has not been determined. At the proposed dose regimen (0.16 mg/0.8 mg/48 mg), the peak concentration of epcoritamab occurred around 3 to 4 days after the first 48 mg epcoritamab SC dose on C1D15 (Figure 6). Plasma concentrations were in general < BLQ for the priming and intermediate dose.

Figure 4: Mean epcoritamab (GEN3013) concentrations in patients for cycle 1 in dose escalating part of GCT3013-014 for (0.16 mg/0.8 mg/24 mg, N=3) and (0.16 mg/0.8 mg/48 mg, N=6)



PopPK estimated that epcoritamab concentrations appeared to reach steady-state by approximately 2 to 3 months after start of each dosing interval (QW, Q2W, or Q4W). PopPK exposure estimates for the 48 mg dose in the target population are summarised in Table 21. Pharmacokinetic results were similar for the LBCL and DLBCL populations.

Table 8: Summary of predicted epcoritamab exposures for 48 mg dose (gMean (CV)) following 0.16/0.8/48 mg dosing regimen, final model 154

Exposure	Cmax,ss (µg/mL)	AUCss (µg/mL*day)	Ctrough,ss (µg/mL)	t1/2 (days)
Week 3 (first dose)	1,9 (111)	9,8 (116)	1,5 (107)	
QWss (week 12)	10,8 (41)	69,3 (44)	8,5 (51)	22,0 (58)
Q2Wss (week 36)	7,5 (44)	82,6 (51)	4,1 (71)	24,4 (72)
Q4Wss (week 60)	4,6 (62)	72,5 (76)	1,2 (126)	22,2 (75)

Abbreviations: AUC_{Week} = area under the concentration time-curve at Week X; $C_{avgWeek}$ = average concentration over 1 week at Week X; $C_{maxWeek}$ = maximum concentrations over a dosing interval at Week X; C_{trWeek} = trough concentrations before dosing at Week X; CV = coefficient of variation; SD = standard deviation; $T_{maxWeek}$ = time to maximum concentrations over a dosing interval at Week X.

Bioequivalence. Initial batches were manufactured via DP process 1. Product manufacturing was successfully scaled up and transferred to the EU manufacturing site DP Process 2.

The commercial product was introduced during the conduct of the Expansion Part of the GCT3013-01 and GCT3013-04 trials during re-supply. Therefore, PK, efficacy, and safety data from the commercial formulation of epcoritamab are included as part of the overall clinical data package.

Distribution

The population PK gMean estimate for the apparent volume of distribution was 23.4 L (81%).

Elimination

PopPK model-based predictions of epcoritamab concentrations, TMDD saturation, and total clearance following the proposed dosing regimen (0.16 mg/0.8 mg/48 mg) are illustrated in Figure 7. Total clearance decreased with increasing concentrations over time following the prime and intermediate doses. After the first full dose of 48 mg epcoritamab on C1D15, mean total clearance approached the linear clearance, suggesting saturation of target-mediated clearance. Despite a decrease in exposures associated with less frequent dosing regimens, such as Q2W and Q4W, target saturation was estimated to be maintained and the total clearance remains close to the linear clearance.

Elimination half-life of epcoritamab was similar following QW, Q2W and Q4W dosing frequency, 22 days (58%), 24 days (72%), and 22 days (75%), respectively.

The population mean estimate for the CL/F was 0.481 L/day (27.3%).

No mass balance and traditional metabolism studies have been conducted because epcoritamab is a IgG1 antibody and as such is mainly metabolised and eliminated through proteolytic degradation into small peptide fragments or amino acids that are ready for renal excretion or recycling into protein synthesis.

Dose proportionality and time dependencies

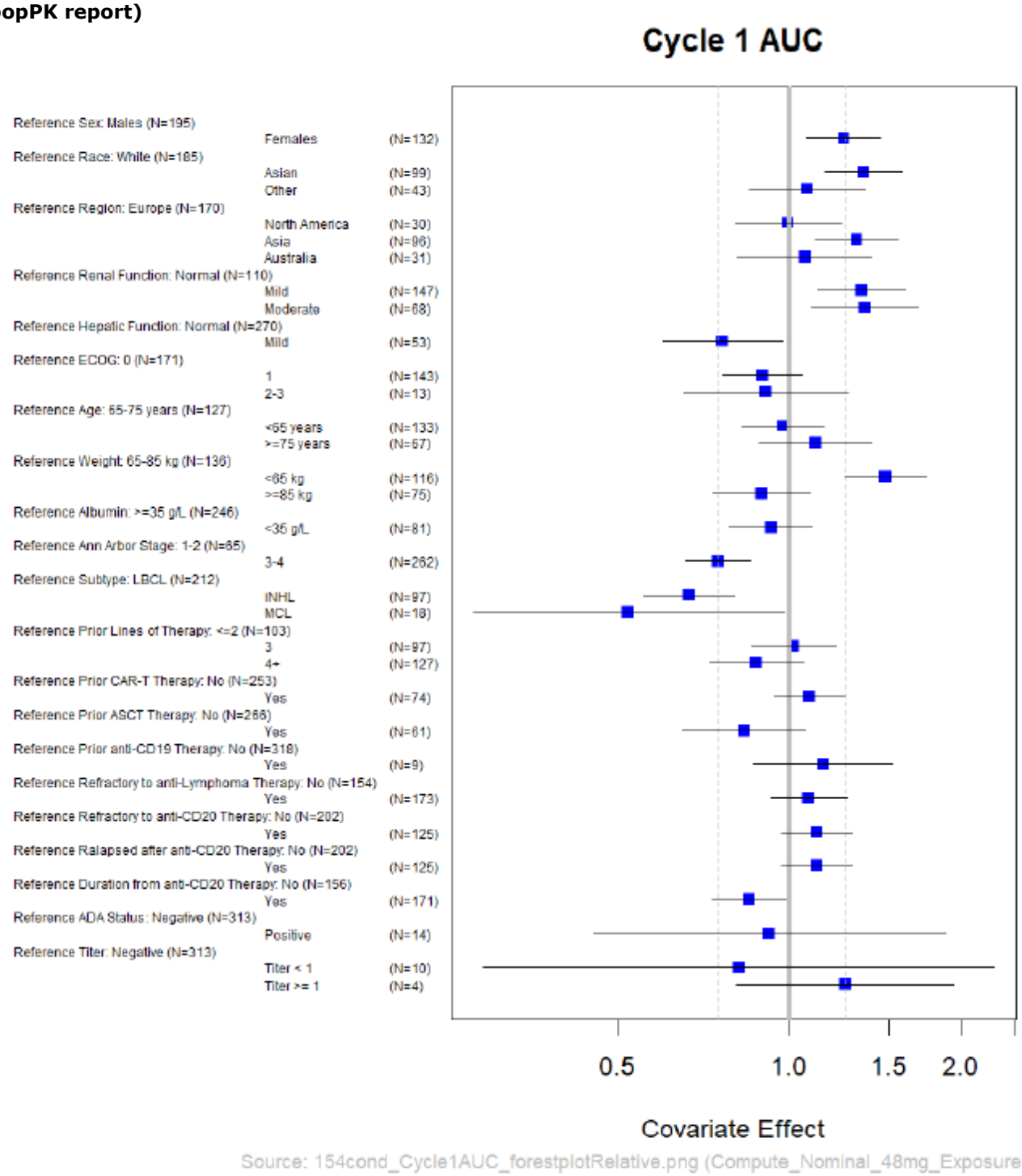
Dose proportionality was evaluated using the intensive PK data from the GCT3013-01 Escalation Part and by popPK analysis. Epcoritamab elimination showed nonlinear characteristics when evaluated using population PK. Exposure increases greater than dose-proportional for dosing regimens with the full dose <24 mg, and approximately dose-proportionally for dosing regimens with the full dose ⩾24 mg.

The final popPK model does not include time dependency of PK parameters. The time dependency of epcoritamab PK was mainly driven by the target mediated drug disposition through time-varying concentration levels at low doses.

Special populations

Special population PK was evaluated by popPK analysis. The initial covariate model included major covariates that usually affect PK of mAbs: body-weight on clearance and volume parameters and age on SC absorption rate constant. When compared to the AUC in subjects with weight 65 to <85 kg, the average AUC during Cycle 1 was 10.6% lower in subjects with weight ⩾85 kg and 47.6% higher in subjects with weight <65 kg. Age was a statistically significant covariate on the absorption rate constant but did not influence other PK parameters. Further covariate analysis (Figure 8) indicated that, after adjusting for body weight and age effects, Asian race, sex, tumour size, ALB, trial effect (04 vs. 01), lymphoma subtypes (iNHL vs. LBCL and MCL vs. LBCL) did not have significant impact on the PK of epcoritamab.

Figure 5: Predicted epcoritamab Cycle 1 AUC by covariates, relative to reference group (popPK report)



Source: 154cond_Cycle1AUC_forestplotRelative.png (Compute_Nominal_48mg_Exposure.R)

Abbreviations: ADA = antidrug antibodies; ASCT = autologous stem cell transplant; AUC = area under the concentration-time curve; CAR-T = chimeric antigen receptor T cell; CD = cluster of differentiation; ECOG = Eastern Cooperative Oncology Group; LBCL = large B-cell lymphoma; N = number of subjects.

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
GCT3013-01 (ESC +EXP)	96/267 (36%)	57/267 (21.3%)	2/267 (0.7%)

	Age 65-74 (Older subjects number /total number)	Age 75-84 (Older subjects number /total number)	Age 85+ (Older subjects number /total number)
GCT3013-01 (ESC +EXP)	96/267 (36%)	57/267 (21.3%)	2/267 (0.7%)
GCT3013-04 (ESC +EXP)	31/60 (51.7%)	7/60 (11.7%)	1/60 (1.7%)

Pharmacokinetic interaction studies

No formal clinical drug-drug interaction studies were performed. As an IgG1 bispecific antibody with a regular IgG1 structure and biochemical characteristics, epcoritamab is expected to be degraded into small peptides and amino acids via catabolic pathways.

Pharmacokinetics using human biomaterials

N/A

Immunogenicity

A total of 14 (4.3%) of 327 PK-evaluable subjects were ADA-positive across all dose levels, and among those, only 4 (1.2%) had titer ⩾1 (1:80 after accounting for dilutions). Among 300 PK-evaluable subjects who received the full dose of 48 mg, only 10 subjects (3.3%) were ADA positive. The onset of immunogenicity was usually after C1D22.

ADA status was not formally investigated as a covariate in the popPK analysis. No meaningful differences in PK were detected between ADA positive and ADA negative subjects based on comparison of eta plots and simulated exposures using the final model.

2.6.2.2. Pharmacodynamics

Mechanism of action

Epcoritamab is a bispecific antibody, recognising the T-cell antigen CD3 and the B-cell antigen CD20. Epcoritamab's mechanism of action is induction of T-cell-mediated cytotoxicity of CD20-expressing cells, and associated T-cell activation and proliferation, upon simultaneous binding to CD20 on target cells and CD3 on T cells.

Primary and Secondary pharmacology

In the subset of subjects with detectable B cells at treatment initiation (23% of the patients from the escalation part and 21% from the expansion part of study GCT3012-01), epcoritamab induced sustained depletion of peripheral B cells (defined as CD19 B-cell counts <10 cells/µL) by C1D15. This was measured based on the presence of the common B cell marker CD19 by flow cytometry in blood. Subjects were considered positive for circulating B cells if more than 10 CD19-positive cells were detected per microliter blood. Transient reductions in total T-cell counts were observed 6 to 14 hours after administration of the priming (C1D1) intermediate (C1D8), and first full dose (C1D15) at all dose levels tested, including the 48 mg full dose level, total T-cell counts recovered before next epcoritamab dosing.

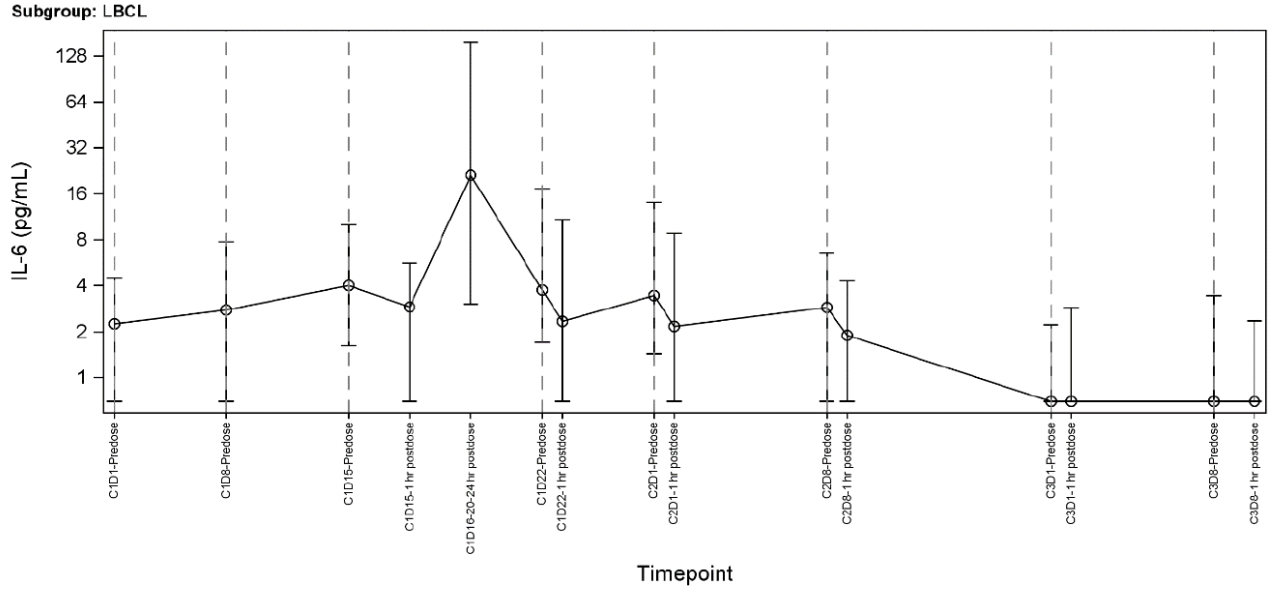
Secondary pharmacology

Cytokines

Epcoritamab step-up dosing resulted in transient elevations of circulating levels of IFN-γ, IL-6, and

TNF-α following administration of the proposed epcoritamab dose regimen (0.16 mg/0.8 mg/48 mg), mostly occurring 1 to 4 days after the first full dose with levels returning to baseline. This is illustrated in Figure 9 for median levels of IL-6 in peripheral blood over time in the aNHL cohort of GCT3013-01 Expansion Part. For IFN-γ IL-10, and TNF-α similar figures can be seen (data not shown).

Figure 6: Median IL-6 Levels in peripheral blood over time in subjects in aNHL Cohort – GCT3013-01 Expansion Part (0.16 mg/0.8 mg/48 mg)



Abbreviations: aNHL = aggressive B-cell non-Hodgkin lymphoma; C = cycle; D = day; DLBCL = diffuse large B-cell lymphoma; IL-6 = interleukin-6; LBCL = large B-cell lymphoma.
Note: For interleukin-6. the lower limit of reporting (LLOR) and upper limit of reporting (ULOR) values were 1.39 and 2848 pg/mL. Values less than 1.39 or greater than 2848 pg/mL are displayed at 0.695 pg/mL and 2848 pg/mL.
Note: The vertical dashed line indicates epcoritamab administration. All samples were collected predose.

Within the tested range for priming and intermediate doses in GCT3013-01 Escalation Part, peak IL-6 concentrations were independent of dose for priming and intermediate doses. There appeared an increasing trend of IL-6 peak concentrations with dose after the first full dose. However, the selected 48 mg full dose (RP2D) produced similar IL-6 peak concentrations compared to lower full doses within the dose range of 6 to 60 mg. Frequency of CRS events was generally the highest following the first full dose and the lowest during the priming dose (C1D1) and the second full dose (C1D22).

Electrocardiograms and pharmacokinetic/pharmacodynamics of QTc intervals

Using the pooled data from both GCT3013-01 and GCT3013-04 the applicant examined the relationship between the baseline-adjusted/corrected change in QTcF intervals and time-matched plasma concentrations of epcoritamab (927 time-matched observations from n=176). The analysis, using a linear mixed effects modelling and to predict 95% CI of QTcF prolongation at mean Cmax values achieved at 48 mg, is adequate. No significant association between epcoritamab concentrations and QTcF was observed in this pooled analysis (P=0.103). At the arithmetic mean predicted Cmax value of 11.7 µg/mL following the proposed dosing regimen of QW doses, QTcF prolongation was predicted to be 0.76 msec, with the 95% CI upper bound of 3.40 msec.

The review of the QTcF data and the PK/pharmacodynamic relationship for epcoritamab revealed no effect of epcoritamab on ΔQTcF. Please refer to the safety section for the assessment of ECGs and clinically significant cardiac AEs.

Exposure-response analyses

Exposure-response analyses were performed to assess the relationships between epcoritamab exposure and efficacy and safety in subjects with (D)LBCL and to support the selected dosing regimen.

The relationship between exposure and ORR and CR rate was analysed with a logistic regression. For PFS and OS, Kaplan-Meier plots were used to compare the survival probability over time for subjects with low and high exposure categorised by the median value of Cycle 1 AUC.

Across the full dose range studied (0.004 to 60 mg), statistically significant ($p<0.05$) relationships between key efficacy endpoints (ORR, CR rate, PFS, and OS) and epcoritamab exposure were observed, ie, higher epcoritamab exposures provided higher ORR/CR rate and longer PFS/OS.

At the proposed 48 mg full dose (i.e., analysis using data only from 48 mg full dose level), the relationships were no longer significant for most efficacy endpoints, but a numerical trend was observed for all the key efficacy endpoints including ORR. Since the logistic regression was no longer statistically significant no multivariate analysis has been conducted.

Exposure-safety analyses were conducted for ⩾ grade 3 TEAEs, serious TEAEs, ⩾ grade 3 neutropenia, ⩾ grade 3 infections, injection site reactions, TEAEs leading to dose delay, TEAEs leading to treatment discontinuation, all grade CRS, ⩾ grade 2 CRS, CRS requiring tocilizumab, ICANS, and CTLS.

Across the dose range studied (0.004 to 60 mg), no increase in incidence of any TEAE category tested was seen with increasing epcoritamab exposure. Importantly, increased epcoritamab exposure did not result in higher incidence of all grade CRS, ⩾ grade 2 CRS, CRS requiring tocilizumab, ICANS, and CTLS across the doses and exposures evaluated.

2.6.3. Discussion on clinical pharmacology

Clinical pharmacology data are available from 2 ongoing clinical trials to support the use of epcoritamab monotherapy in LBCL and DLBCL. The epcoritamab clinical pharmacology program included the evaluation of multiple dose PK, effects of relevant intrinsic and extrinsic covariates on epcoritamab exposure evaluated by a popPK approach, exposure-response analysis, biomarker analyses, QT prolongation potential, and immunogenicity.

No dedicated studies have been conducted to evaluate metabolism, in patients with renal or hepatic impairment, drug interactions and QT prolongation. This is considered acceptable because epcoritamab is a IgG1 therapeutic protein and no direct effects on these populations/issues are to be expected. QTc prolongation potential was investigated using time-matched PK and ADA/ECG measurements in the clinical studies to confirm the absence of an effect.

RP2D was investigated in the dose escalation phase of the pivotal study GCT3013-01.For further considerations regarding posology, please see section 3.3.5 Discussion on clinical efficacy.

Methods Both PK and immunogenicity assays are adequately validated, and the provided validation documentation and principle of the employed methods are considered appropriate and in accordance with relevant guidelines.

Two bioanalytical assays SMCIA-139 and ECLIA-139 were used to analyse epcoritamab in human plasma in the dose escalating part of study GCT3013-01. SMCIA-139 method was used early in the study to evaluate low dose epcoritamab plasma concentrations. Cross-validation showed differences between the two bioanalytical methods, with on average higher concentration for the ECLIA-139 method. In this dossier only data with bioanalytical ECLIA-139 method have been presented. It is agreed that only these data can be used for the popPK analysis, however, there is no PK info with the

ECLIA-139 method on the priming and intermediate doses. In addition, there is some uncertainty about the ability of the popPK model to describe the dose dependency adequately. For these reasons, the applicant is requested to present the non-compartmental PK results of the SMCIA-139 method. However, there was no apparent dose response over the dose range 1.5 – 48 mg with the SMCIA-139 and these data cannot be used to strengthen the sparse data available at lower doses than ≤ 12 mg for the ECLIA-139 method. Since only one full dose of 48 mg is proposed and there is no clear exposure-response relationship for both efficacy and safety, the additional information that could have been obtained with the SMCIA-139 method is not pivotal.

popPK analysis Model development, performance evaluation and reporting of the popPK model was good and in line with the guideline. Data on absorption rate were mainly based on the PK sampling during the first cycle, because at later cycles PK sampling was confined to predose sampling and 1h after SC administration. Since the absorption rate and the elimination rate are long, the values for predose and 1h after SC are very similar. Therefore, there is some uncertainty with the estimation of Cmax values at steady-state. Further, some clarification is requested regarding incorporation in the analyses of blood transfusions, subjects with interfering plasma levels and whether impact of CRS grade>2 has been evaluated. It was shown that the pharmacokinetic data in subjects with blood transfusion (N=58) overlapped with those who had no blood transfusion (N=269), which can be expected since the transfusion volume was less than one tenth of the estimated Volume of distribution. In addition, it was shown that CRS ≥ Grade 2, had no impact on the pharmacokinetics: subjects with CRS ≥ Grade 2 (N=83) had similar pharmacokinetics as subjects with CSR<grade 2 (N=244).

Plasma concentrations of epcoritamab dosed 48 mg were adequately described by a two-compartment target mediated drug disposition (TMDD) model with the first order SC absorption. However shrinkage of various parameters such as clearance was rather high i.e. 34% in the final model, which indicate that the PK data are less informative at the individual level. There was a trend of underestimation of epcoritamab concentrations at doses ≤12 mg suggesting that TMDD might be overestimated. This was further strengthened that the sensitivity analysis for samples <BLQ method changed the TMDD parameters Base and Kss with 30-90%. Therefore, there is uncertainty concerning the population predictions of the final model for the low doses <12 mg used in the exposure-efficacy analysis. Since the impact of TMDD at a dose of 48 mg epcoritamab is low compared to the non-specific clearance, popPK model is fit for purpose to predict epcoritamab exposures for 48 mg dose and no adjustment of the popPK model is needed. The popPK model is considered fit for purpose to describe the pharmacokinetics following the 48 mg dose and to assess the impact of covariates on the PK of epcoritamab.

Drug product During development, epcoritamab was manufactured at two different sites. No dedicated PK comparison has been conducted between the batches produced at the different sites. The commercial product has been used in the clinical studies. As estimated by popPK the bioavailability is 9% less for process B and the clearance is 6% higher. The two process batches result in fully overlapping epcoritamab concentrations, indicating no impact of manufacturing site on the PK.

Pharmacokinetics

Pharmacokinetic results were similar for the LBCL and DLBCL populations.

In patients, the PK profile of SC epcoritamab was characterised by slow absorption and linear non-specific elimination and target mediated elimination. At the 48 mg dose, the non-specific elimination mediated by FcRn receptor is predominant. At lower doses, target mediated clearance might be more predominant. Elimination half-life of epcoritamab as estimated by popPK analysis was 22-24 days for QW, Q2W and Q4W dosing regimens with 48 mg. The population PK gMean estimate for the apparent volume of distribution was 24.3 L (81%), which is somewhat higher than usual for human IgG1

antibody but the uncertainty in the estimate was high. Overall, the pharmacokinetics of epcoritamab are in line with other therapeutic IgG1 antibodies.

Absorption rate with the geometric mean tmax ranged from approximately 3 to 4 days across doses. This is an absorption rate commonly seen for IgG molecules administered subcutaneously. Absorption rate declined with age, as would be expected for SC administration of mAbs. In younger (33.3 years old, the 2.5th percentile) and older (82 years old, the 97.5th percentile) subjects, ka was 39.9% higher and 11.0% lower compared to 65 years old subjects, respectively. However, the predicted epcoritamab AUC exposures in older subjects are similar to those for younger subjects.

Absolute bioavailability of epcoritamab SC has not been determined, but in general absolute bioavailability of antibodies following the SC route is high (~70%, Sánchez-Félix et al., Advanced Drug Delivery Reviews 2020). High absolute bioavailability was also indicated in monkeys (see non-clinical AR). There was no relevant difference in epcoritamab exposure following injection in the abdomen and thigh. Therefore, the text in the SmPC that epcoritamab can be administered in the abdomen or thigh, is acceptable. Overall, pharmacokinetics of epcoritamab can be characterised sufficiently without precise estimation on the absolute bioavailability.

Similar to other therapeutic antibodies, body weight was a significant covariate affecting the PK of epcoritamab. For the extreme values of weight (44.7 kg and 110 kg, defined as 2.5th and 97.5th percentiles of weight distribution in the analysis population) AUC at week 12 was 60% higher and 30% lower, respectively compared to subjects weighing 75 kg. Response rate was similar over the dose range 12-60 mg and also no dose response for safety was apparent; efficacy and safety was generally consistent across these studied body weight categories. Therefore, the difference in exposures among different weight groups are considered not clinically meaningful.

None of the other covariates, including sex, race (White, Asian, and Other), laboratory values, renal and hepatic function, ECOG score, tumour size and lymphoma subtypes, and geographic region (Asia and North America versus Europe) had a statistically significant effect on epcoritamab PK after accounting for the body weight. The effects on epcoritamab exposure measures were <25% difference with the average exposure. Potential impact of ADAs on PK was only investigated by popPK model exercises, no impact on the pharmacokinetics was apparent but the dataset with ADA positive samples was low.

No formal clinical drug-drug interaction studies were performed. Epcoritamab causes a transient release of cytokines and thus may reduce enzyme activity of several CYP enzymes. Treatment of CRS grade >2 with tocilizumab counteracts the potential effects of elevated levels of IL-6. Given the transient character of the IL-6 elevations and the poor predictability when these elevations occur, it is agreed that a clinical study to evaluate the potential interaction is difficult to conduct. Moreover, the impact of elevated IL-6 /cytokines on metabolism of other medicines are generally modest < 2-fold (Gatti, Clinical Pharmacokinetics (2022)). This might be relevant for co-administered medicines with a narrow therapeutic exposure range. The text in the SmPC section 4.5 is considered acceptable.

Pharmacodynamics

Epcoritamab's mechanism of action is induction of T-cell-mediated cytotoxicity of CD20-expressing cells, and associated T-cell activation and proliferation, upon simultaneous binding to CD20 on target cells and CD3 on T cells. The MoA is considered relevant for the therapeutic setting. The primary and secondary pharmacology was analysed by measuring B-cell detection, T-cell counts and cytokine levels and by assessing the potential of epcoritamab to impact cardiac repolarization.

B-cells / T-cells. Circulating B cell counts was assessed based on the presence of the common B cell marker CD19 by flow cytometry in blood. Subjects were considered positive for circulating B cells if more than 10 CD19-positive cells were detected per microliter blood. There is clinical evidence that

epcoritamab induces and maintains B-cell depletion, however only a very small sample of patients were available for evaluation (GCT3013-01 escalation part N=18/65 patients (28%) and expansion part N=33 (21.0%)). Epcoritamab is also associated with transient reductions in T-cell count margination followed by an increase in T cell counts in circulation.

For both GCT3013-01 and GCT3013-04, further exploratory tumour/bone marrow biomarker analyses are under consideration in order to identify potential biomarkers predictive of response or resistance, and mechanisms of tumour response and/or treatment-induced changes in the immune microenvironment. The results will be presented for review when finalised.

Cytokines. A transient elevation in circulating levels of IL-6, IFN-γ, IL-10, and TNF-α was observed. CRS may be seen with epcoritamab treatment, mainly after the first full dose, but thereafter is also possible. Between effective doses (12-60 mg) the occurrence of CRS based on the IL-6 peak concentration is comparable between doses. The role of the priming and intermediate dose has not elucidated and neither the adequacy of the height of these doses could be confirmed.

QTcF- It is agreed with the applicant that a thorough QT/QTc study is in principle not necessary, as large monoclonal antibodies have a low likelihood of direct ion channel interactions (ICH guideline E14/S7B: clinical and Nonclinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential - questions and answers EMA/CHMP/ICH/415588/2020). The review of the QTcF data and the PK/pharmacodynamic relationship for epcoritamab revealed no effect of epcoritamab on ΔQTcF.

Exposure-response. The objectives for exposure-response analysis were descriptive, so no high impact analyses. The exposure-response analyses identified exposure as a significant factor when including the full dose range studied (0.004 to 60 mg) but not when considering the proposed dosing regimen with 48 mg full dose. Dose response data indicated that ORR and CR were similar in the dose range 12-60 mg. Exposure-response for safety across the full dose range did not identify statistically significant relationships. These exposure-response analyses support the 48 mg as a dose with acceptable efficacy and safety, but also indicates that other doses might be equally effective/safe (see also comments at dose finding in efficacy part of AR). The applicant is encouraged to further explore/investigate potential epcoritamab exposure-response relationships when other dosing regimen are evaluated.

Immunogenicity. Using the proposed dosing regimen, 11/361 subjects with LBCL/DLBCL were ADA positive on treatment in studies GCT3013-01 and GCT3013-04. Neutralising antibodies have not been evaluated but considering the low incidence of ADAs <5% of patients having (transiently) ADA expression, this is considered acceptable, but the absence of measurement is acknowledged in the SmPC section5.1.

2.6.4. Conclusions on clinical pharmacology

Characterisation of clinical pharmacology of epcoritamab is based on data from two ongoing clinical trials in subjects with LBCL/DLBCL. The pharmacokinetics of epcoritamab are in line with other therapeutic IgG1 antibodies. Overall, the information provided can be considered satisfactory and has been reflected in the SmPC section 5.2.

Further, immunogenicity needs to be continued to be evaluated in (future) clinical studies.

2.6.5. Clinical efficacy

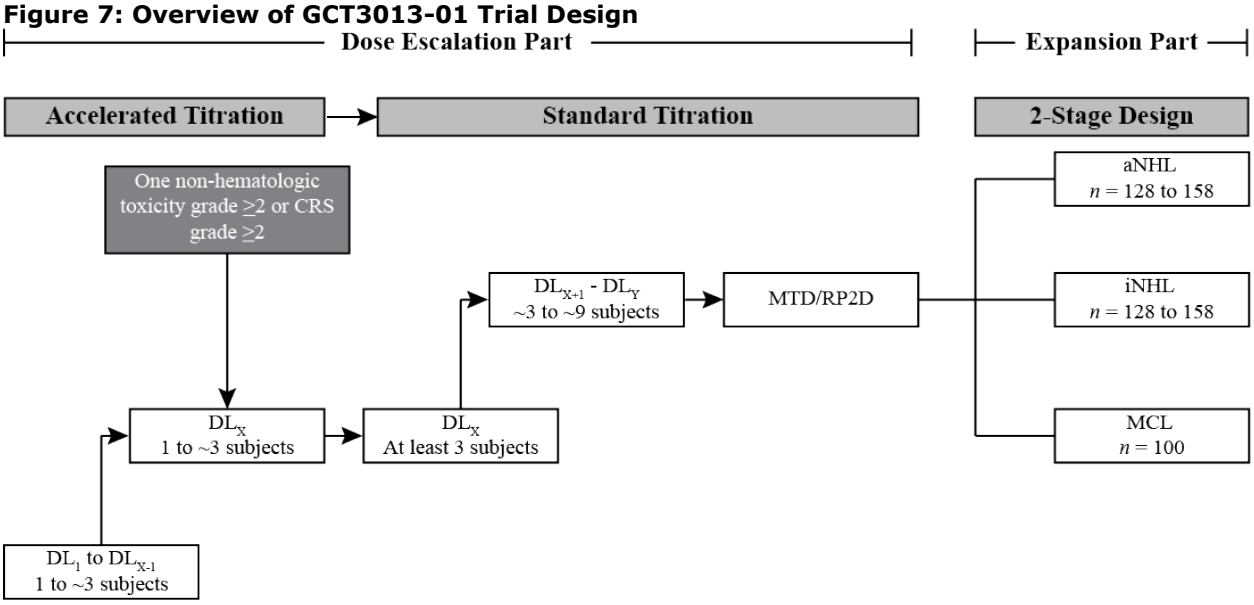
2.6.5.1. Dose response study(ies)

GCT3013-01 Trial – dose escalation part

Methods

This is a First-in-human (FIH), open-label, phase 1/2 trial in subjects aged 18 years or older with relapsed, progressive and/or refractory (R/R) mature B-cell lymphoma. The trial includes 2 parts: a Dose Escalation Part and an Expansion Part. The trial design is illustrated in Figure 10.

Figure 7: Overview of GCT3013-01 Trial Design



Abbreviations: aNHL = aggressive B-cell non-Hodgkin lymphoma subtypes; CRS = cytokine release syndrome graded according to (Lee et al., 2019); DL = dose level; iNHL = indolent B-cell non-Hodgkin lymphoma subtypes; MCL = mantle cell lymphoma; MTD = maximum tolerated dose; RP2D = recommended phase 2 dose; X = the dose level where the trigger (grade 2 non hematological toxicity etc.) is observed: switch from single subject cohort to 3 subject cohort

The aim of the Dose Escalation Part of this trial was to establish the maximum tolerated dose (MTD) and the recommended phase 2 dose (RP2D) of epcoritamab. The primary endpoint was the incidence of dose limiting toxicities (DLTs) and safety to determine the MTD and RP2D in subjects with R/R B-cell non Hodgkin lymphoma (B-NHL). Secondary efficacy endpoints included overall response rate (ORR), complete response (CR), partial response (PR), duration of response (DOR), progression free survival (PFS), time to next (anti-lymphoma) treatment (TTNT), and overall survival (OS). Responses were assessed by the investigator only according to the Lugano criteria.

Doses were administered in 2 titration parts: an accelerated titration part and a standard titration part. The accelerated titration part consisted of single patient cohorts which could be expanded by up to 2 additional subjects (at each investigated dose) for the purpose of obtaining additional PK and pharmacodynamic biomarker data. Once non-hematologic toxicity grade ≥2 according to NCI-CTCAE version 5.0 or cytokine release syndrome (CRS) grade ≥2 according to the grading by Lee et al. was observed at a dose level, the cohort was expanded with an additional 2 patients and the cohort sizes for the remaining dose levels were 3 patients. After that the standard titration part followed, where cohorts were allowed to include only 2 patients who were DLT-evaluable, provided that neither of the 2 patients experienced any grade ≥2 toxicity during the DLT evaluation period, which was defined as the first 4 weeks (i.e., 28 days after the first dose of epcoritamab). Over-recruitment by 1 subject was

allowed, so that each 3-patient cohort could consist of 2 to 4 DLT-evaluable patients. The Dose Escalation Part of the trial was performed following a modified approach from the Bayesian Optimal Interval BOIN design (Yuan et al., 2016).

The priming dose was investigated in 'parallel evaluation' cohorts (up to 10 additional patients) where the new priming dose was assessed following a previously declared safe full dose by the data monitoring committee (DMC) and Safety Committee. This continued until the new priming dose was declared safe based on the 'priming dose escalation' stopping criteria: if ≥2 out of 6 patients with CRS Grade 2 or any CRS Grade 3 or 4 were observed in the 'parallel evaluation' cohorts, that further escalation of the priming dose was stopped.

The MTD was defined as the highest dose level with an observed DLT rate lower than the target toxicity level of 30%. Selection of the RP2D was based on review of the available efficacy and safety information (including adverse events (AEs) and safety laboratory values, and observations made after the end of the DLT evaluation period) and was allowed to be lower than the MTD.

During the Dose Escalation Part of the trial, epcoritamab was administered in 28-day cycles as follows:

- Cycles 1 and 2: Days 1, 8, 15, and 22 per week (QW)
- Cycles 3 to 6: Days 1 and 15 per 2 weeks (Q2W)
- Cycles 7 and beyond until unacceptable toxicity, PD, or withdrawal of consent: Day 1 (Q4W)

DLTs were defined as Grade 5 toxicity, CRS Grade 4 and 3 (if not improved within 48 hours), neutropenia Grade 4 lasting > 7 days, febrile neutropenia grade ≥ 3 lasting > 2 days, thrombocytopenia grade 4 lasting > 7 days and non-hematological toxicity grade 3 or higher excluding certain events which resolved in time/ respond to therapy, CRS, fatigue if present at baseline and alopecia.

The patient population enrolled in the escalation part of the GCT3013-01 trial were aged 18 years or older with an ECOG performance status 0, 1 or 2, and had documented evidence of CD20-positive mature B-cell neoplasm according to WHO classification 2016 or 2008. Non-Hodgkin (NHL) subtypes allowed were DLBCL, high grade B-cell lymphoma (HGBL), primary mediastinal B-cell lymphoma (PMBCL), follicular lymphoma (FL), and mantle cell lymphoma (MCL), small lymphocytic lymphoma (SLL), and marginal zone lymphoma (MZL; nodal, extranodal or mucosa associated). Subjects had relapsed, progressive and/or refractory disease following treatment with an anti-CD20 monoclonal antibody (mAb; e.g., rituximab) potentially in combination with chemotherapy and/or relapsed after autologous stem cell rescue and had exhausted or were ineligible for all standard therapeutic options. Subjects had at least 1 measurable site of disease based on CT/MRI.

During the Dose Escalation Part of the trial, epcoritamab priming doses ranging from 0.004 (MABEL) to 0.16 mg, intermediate doses ranging from 0.25 to 1.6 mg, and full doses ranging from 0.0128 to 60 mg doses were explored in subjects with R/R B-NHL. In total 17 cohorts (12 cohorts, 5 parallel evaluations) with different priming/intermediate and full doses were evaluated (Table 22).

Table 9: Planned Doses by Cohort – GCT3013-01 Dose Escalation Part

Cohort	Cycle 1 Epcoritamab Doses (in mg)			
	Priming	**Intermediate**	**First Full**	**Second Full**
1	0.004	NA	0.0128	0.0128
2	0.0128	NA	0.04	0.04
3	0.04	NA	0.12	0.12
3a	0.04	NA	0.38	0.38
4	0.12	NA	0.38	0.38
5	0.04	NA	0.76	0.76
6	0.04	0.25	1.5	1.5
7	0.04	0.5	3	3
8	0.04	0.5	6	6
8a	0.08	0.5	6	6
9	0.04	0.8	12	12
9a	0.08	1.6	12	12
10	0.04	0.8	24	24
10a	0.16	0.8	24	24
11	0.08	0.8	48	48
11a	0.16	0.8	48	48
12	0.16	0.8	60	60

Abbreviations: NA = not applicable
Notes: To bridge the gap between priming and continuously escalating full doses, an intermediate dose of epcoritamab was added prior to dosing at the 1.5 mg full dose level (beginning with Cohort 6). The last dose in Cycle 1 (ie, full dose) was continued in Cycle 2 and onwards.
Cohorts ending with 'a' were intended for parallel evaluation.
Data cutoff date: 31 Jan 2022
Source: Table 14.1.11

An integrated, model-based approach was implemented to support the selected RP2D. This approach relied on the safety, efficacy, PK, and pharmacodynamic data from the Dose Escalation Part in combination with preliminary population-PK modeling, PK/ pharmacodynamic modeling, exposure-response analysis, and exposure-safety analysis.

Of note, a dose optimisation part was added to the GCT3013-01 protocol to evaluate additional priming and intermediate dosing regimens to explore the potential for further reduction in incidence and/or severity of CRS; this part of the trial has not yet been initiated and no data are available.

The rationale for the SC route of epcoritamab administration was based on its lower C_{max} value and lower peak cytokine levels, but comparable B-cell depletion compared to IV administration at the same doses (mg/kg) in the nonclinical studies. For the initial treatment cycles, more frequent (QW) dosing of

epcoritamab was selected due to the potential for higher target-mediated clearance due to higher tumor burden. The rationale for decreasing the dose frequency to Q2W in Cycles 3 to 6 and Q4W thereafter, is based on the assumption that tumor burden will decrease over time, similar to the B-cell depletion observed in peripheral blood and lymph nodes of cynomolgus monkeys.

Per the original protocol (15 Nov 2017), subjects were premedicated with corticosteroids (one day), antihistamines, and antipyretics 30 to 120 minutes prior to the first 4 doses of epcoritamab. For later doses of epcoritamab, premedication and CRS prophylaxis were optional. Beginning with Protocol Amendment 3 (dated 15 Apr 2019), corticosteroids were administered following epcoritamab administration on Days 1, 2, and 3 for the 1st and/or 2nd epcoritamab dose in Cycle 1. Beginning with Amendment 5 (dated 04 Nov 2019) starting with cohort 7, corticosteroids were given for each of the 4 doses of epcoritamab in Cycle 1 (i.e., Days 1, 8, 15 and 22) with the goal of further mitigating the incidence and severity of CRS. In Protocol Amendment 06, Version 8.0 (dated 08 Jun 2020; only applicable to expansion cohort) the corticosteroid prophylactic plan was increased from 3 consecutive days to 4 consecutive days (i.e., days 1 to 4) in Cycle 1. If CRS ≥ grade 2 occurred following the 4th epcoritamab administration on C1D22, consecutive corticosteroids continued in Cycle 2 until CRS was resolved.

Results

The first subject signed informed consent on 26 Jun 2018. At the data cut-off of 31 Jan 2022 a total of 73 subjects were enrolled (subjects who signed informed consent) and 68 subjects were treated with epcoritamab at full doses ranging from 0.0128 mg to 60 mg in the Dose Escalation Part. Of the 68 treated subjects, 60 (88.2%) subjects had discontinued treatment. The most frequent reasons for treatment discontinuation were disease progression (51 [75.0%] subjects) and decision to proceed with transplant following a response to epcoritamab (6 [8.8%] subjects). Protocol deviations were reported in 8 (11.8%) subjects. These deviations were related to dosing (of concurrent medication and priming dose) and enrollment criteria (4 [5.9%] subjects each).

In the overall group, 45 [66.2%] subjects were male. The median age was 67.5 years (range: 21, 84). Forty-six (67.6%) had DLBCL, 3 (4.4%) HGBL, 1 (1.5%) PMBCL, 12 (17.6%) with FL and other in 6 (8.9%).

Efficacy

Table 10: Disease Response Based on Investigator Assessment, Lugano Criteria – Dose Escalation Part (Full Analysis Set)

	Epcoritamab full dose (mg)					
	≤6 mg (N=36)	**12 mg** (N=7)	**24 mg** (N=10)	**48 mg** (N=12)	**60 mg** (N=3)	Total (N=68)
Overall response rate (ORR)[a]	9 (25.0%)	5 (71.4%)	5 (50.0)	8 (66.7%)	3 (100%)	30 (44.1%)
95% CI[b]	(12.1, 42.2)	(29.0, 96.3)	(18.7, 81.3)	(34.9, 90.1)	(29.2, 100)	
Complete response (CR) rate	5 (13.9%)	5 (71.4%)	4 (40.0%)	3 (25.0%)	3 (100%)	20 (29.4%)
95% CI[b]	(4.7, 29.5)	(29.0, 96.3)	(12.2, 73.8)	(5.5, 57.2)	(29.2, 100)	
Best overall response, n (%)						
Complete response (CR)	5 (13.9%)	5 (71.4%)	4 (40.0%)	3 (25.0%)	3 (100%)	20 (29.4%)
Partial response (PR)	4 (11.1%)	0	1 (10.0%)	5 (41.7%)	0	10 (14.7%)
Stable disease	6 (16.7%)	1 (14.3%)	1 (10.0%)	0	0	8 (11.8%)
Progressive disease (PD)	20 (55.6%)	1 (14.3%)	4 (40.0%)	1 (8.3%)	0	26 (38.2%)
Not evaluable (NE)[c]	1 (2.8%)	0	0	3 (25.0%)	0	4 (5.9%)

Abbreviations: CI = confidence interval
CR+PR
95% CI was based on Clopper and Pearson method
Subjects did not have a postbaseline response assessment
Data cutoff date: 31 Jan 2022
Source: Table 14.2.1

After a median follow-up of 12.2 months, the median DOR was 18.1 months (95% CI: 4.2, NR). For the 48 mg dose level (N=12), after a median follow-up of 12.4 months, the median DOR was 6.0 months (range: 1.3, NR).

After a median follow-up of 12.2 months, the median PFS was 2.6 months (95% CI: 1.6, 4.0). For the 48 mg dose level (N=12), after a median follow-up of 12.4 months, the median PFS was 2.8 months (95% CI: 1.0, 11.8). The median OS was 12.2 (4.3, 18.5) months (median follow up not provided).

Safety

In total, 29 subjects were included in the dose determining analysis set (DDS). The priming dose was escalated from 0.004 mg to 0.16 mg, the intermediate dose was escalated from 0.25 mg to 1.6 mg, and the full dose level was escalated from 0.0128 mg to 60 mg. None of the subjects in the DDS experienced DLTs in any of the dose levels tested (0.0128 mg to 60 mg) and the MTD was not identified.

A review of data from Cohorts 1 through 11 indicated the proposed priming/intermediate/full dosing regimen of 0.16 mg/0.8 mg/48 mg regimen had similar or numerically lower rates of CRS (compared to other dosing regimens (e.g., comprising full doses of 24 mg and 60 mg). Results from the PK/pharmacodynamic evaluation of cytokine (IL-6) data and modeling analysis suggested further escalation of the priming and intermediate doses beyond the current priming/intermediate doses (0.16 mg/0.8 mg) could have potentially led to an increased risk of cytokine release syndrome (CRS).

As of the data cutoff date, all 68 subjects in the Dose Escalation Part had experienced at least 1 TEAE. Refer to Table 24.

Table 11: Summary of Treatment-Emergent Adverse Events- Dose Escalation Part (Safety Set)

Number of subjects, n (%)	Epcoritamab full dose (mg)					
	≤6 mg (N=36)	**12 mg** (N=7)	**24 mg** (N=10)	**48 mg** (N=12)	**60 mg** (N=3)	**Total** (N=68)
Number of subjects with ≥1						
TEAE	36 (100%)	7 (100%)	10 (100%)	12 (100%)	3 (100%)	68 (100%)
Related TEAE	33 (91.7%)	7 (100%)	10 (100%)	12 (100%)	3 (100%)	65 (95.6%)
Grade 3 and higher TEAE	27 (75.0%)	5 (71.4%)	7 (70.0%)	11 (91.7%)	2 (66.7%)	52 (76.5%)
Grade 3 and higher related TEAE	15 (41.7%)	4 (57.1%)	4 (40.0%)	6 (50.0%)	2 (66.7%)	31 (45.6%)
TEAE by worst toxicity grade						
Grade 1	2 (5.6%)	1 (14.3%)	0	0	0	3 (4.4%)
Grade 2	7 (19.4%)	1 (14.3%)	3 (30.0%)	1 (8.3%)	1 (33.3%)	13 (19.1%)
Grade 3	14 (38.9%)	4 (57.1%)	5 (50.0%)	6 (50.0%)	1 (33.3%)	30 (44.1%)
Grade 4	6 (16.7%)	0	0	2 (16.7%)	1 (33.3%)	9 (13.2%)
Grade 5	7 (19.4%)	1 (14.3%)	2 (20.0%)	3 (25.0%)	0	13 (19.1%)
Serious TEAEs	24 (66.7%)	3 (42.9%)	6 (60.0%)	10 (83.3%)	2 (66.7%)	45 (66.2%)
Related serious TEAEs	8 (22.2%)	2 (28.6%)	5 (50.0%)	7 (58.3%)	2 (66.7%)	24 (35.3%)
TEAE leading to treatment discontinuation	7 (19.4%)	1 (14.3%)	2 (20.0%)	1 (8.3%)	0	11 (16.2%)
TEAE leading to dose delay	16 (44.4%)	3 (42.9%)	3 (30.0%)	8 (66.7%)	3 (100%)	33 (48.5%)
Fatal TEAEs	7 (19.4%)	1 (14.3%)	2 (20.0%)	3 (25.0%)	0	13 (19.1%)
AESI						
CRS	18 (50.0%)	4 (57.1%)	8 (80.0%)	8 (66.7%)	2 (66.7%)	40 (58.8%)
NS	1 (2.8%)	2 (28.6%)	1 (10.0%)	0	0	4 (5.9%)
CTLS	0	0	0	1 (8.3%)	0	1 (1.5%)

The most frequently reported (≥20% subjects overall) treatment emerging AEs (TEAEs) by preferred term (PT) during the Dose Escalation Part were CRS (40 [58.8%] subjects), injection-site reaction (33 [48.5%] subjects), fatigue (32 [47.1%] subjects), pyrexia (excluding the events reported as a symptom of concurrent CRS; 20 [29.4%] subjects), and diarrhea (18 [26.5%] subjects). No Grade 3 or higher CRS events were reported. Overall, 9 (13.6%) subjects had positive anti-drug antibodies (ADA) at baseline and 12 (18.2%) subjects had positive ADA on treatment. Presence of neutralizing antibodies was not evaluated at this time.

The proposed priming/intermediate/full dose of 0.16 mg/0.8 mg/48 mg (RP2D) regimen had similar or rates of CRS compared to those observed in other dosing regimens containing a full dose of 24 mg and 60 mg (Table 25).

Table 12: Summary of CRS Events by Dosing Period – Dose Escalation Part (Safety Set)

Number of subjects, n (%)	**Dosing period**				
	Priming	**Intermediate**	**First full**	**Second full**	**Third full and after**
Priming/Full = (0.04/0.12 mg) - Cohort 3	**N=4**		**N=4**	**N=4**	**N=3**
Subjects with ≥1 CRS event	3 (75.0%)		3 (75.0%)	**0**	**0**
Number of CRS events[a]	3		3	**0**	**0**
Grade 1	2 (66.7%)		1 (33.3%)	**0**	**0**
Grade 2	1 (33.3%)		2 (66.7%)	**0**	**0**
Priming/ Full =(0.04/0.76 mg) - Cohort 5	**N=7**		**N=7**	**N=7**	**N=7**
Subjects with ≥1 CRS event	1 (14.3%)		4 (57.1%)	**0**	1 (14.3%)
Number of CRS events[a]	1		5	0	1
Grade 1	**0**		3 (60.0%)	**0**	1 (100%)
Grade 2	1 (100%)		2 (40.0%)	**0**	**0**
Priming/Intermediate/Full =0.04/0.25/1.5 mg) - Cohort 6	**N=5**	**N=5**	**N=4**	**N=4**	**N=4**
Subjects with ≥1 CRS event	**0**	**0**	1 (25.0%)	2 (50.0%)	1 (25.0%)
Number of CRS events[a]	0	0	1	2	2
Grade 1	**0**	**0**	1 (100%)	2 (100%)	2 (100%)
Grade 2	**0**	**0**	**0**	**0**	**0**
Priming/Intermediate/Full = 0.04/0.5/3 mg – Cohort 7*	**N=6**	**N=6**	**N=6**	**N=6**	**N=5**
Subjects with ≥1 CRS event	**0**	**0**	2 (33.3%)	1 (16.7%)	**0**
Number of CRS events[a]	0	0	2	1	0
Grade 1	**0**	**0**	1 (50.0%)	**0**	**0**
Grade 2	**0**	**0**	1 (50.0%)	1 (100%)	0

Number of subjects, n (%)	Dosing period				
	Priming	**Intermediate**	**First full**	**Second full**	**Third full and after**
Priming/Intermediate/Full = 0.04/0.5/6 mg – Cohort 8	**N=7**	**N=6**	**N=6**	**N=5**	**N=4**
Subjects with ≥1 CRS event	1 (14.3%)	2 (33.3%)	3 (50.0%)	2 (40.0%)	1 (25.0%)
Number of CRS events[a]	1	2	4	3	5
Grade 1	1 (100%)	2 (100%)	3 (75.0%)	3 (100%)	5 (100%)
Grade 2	**0**	**0**	1 (25.0%)	**0**	**0**
Priming/Intermediate/Full = 0.08/0.5/6 mg – Cohort 8a	**N=2**	**N=2**	**N=2**	**N=2**	**N=2**
Subjects with ≥1 CRS event	**0**	2 (100%)	1 (50.0%)	**0**	**0**
Number of CRS events[a]	0	2	1	0	0
Grade 1	**0**	1 (50.0%)	1 (100%)	**0**	**0**
Grade 2	**0**	1 (50.0%)	**0**	**0**	**0**
Priming/Intermediate/Full = 0.04/0.8/12 mg – Cohort 9	**N=3**	**N=3**	**N=3**	**N=3**	**N=3**
Subjects with ≥1 CRS event	**0**	1 (33.3%)	2 (66.7%)	**0**	**0**
Number of CRS events[a]	**0**	1	2	**0**	**0**
Grade 1	**0**	1 (100%)	1 (50.0%)	**0**	**0**
Grade 2	**0**	**0**	1 (50.0%)	**0**	**0**
Priming/Intermediate/Full = 0.08/1.6/12 mg – Cohort 9a	**N=4**	**N=4**	**N=4**	**N=3**	**N=3**
Subjects with ≥1 CRS event	**0**	2 (50.0%)	1 (25.0%)	**0**	**0**
Number of CRS events[a]	**0**	2	1	**0**	**0**
Grade 1	**0**	1 (50.0%)	**0**	**0**	**0**
Grade 2	**0**	1 (50.0%)	1 (100%)	**0**	**0**
Priming/Intermediate/Full = 0.04/0.8/24 mg – Cohort 10	**N=6**	**N=6**	**N=6**	**N=6**	**N=6**
Subjects with ≥1 CRS event	1 (16.7%)	3 (50.0%)	3 (50.0%)	**0**	1 (16.7%)
Number of CRS events[a]	1	3	3	**0**	1
Grade 1	**0**	2 (66.7%)	2 (66.7%)	**0**	**0**

Number of subjects, n (%)	Dosing period				
	Priming	**Intermediate**	**First full**	**Second full**	**Third full and after**
Grade 2	1 (100%)	1 (33.3%)	1 (33.3%)	**0**	1 (100%)
Priming/Intermediate/Full = 0.16/0.8/24 mg – Cohort 10a	**N=4**	**N=4**	**N=4**	**N=4**	**N=3**
Subjects with ≥1 CRS event	1 (25.0%)	2 (50.0%)	1 (25.0%)	**0**	**0**
Number of CRS events[a]	1	2	1	**0**	**0**
Grade 1	1 (100%)	2 (100%)	**0**	**0**	**0**
Grade 2	**0**	**0**	1 (100%)	**0**	**0**
Priming/Intermediate/Full = 0.08/0.8/48 mg – Cohort 11	**N=3**	**N=3**	**N=2**	**N=2**	**N=2**
Subjects with ≥1 CRS event	1 (33.3%)	1 (33.3%)	2 (100%)	**0**	**0**
Number of CRS events[a]	1	1	2	**0**	**0**
Grade 1	1 (100%)	1 (100%)	1 (50.0%)	**0**	**0**
Grade 2	**0**	**0**	1 (50.0%)	**0**	**0**
Priming/Intermediate/Full = 0.16/0.8/48 mg (RP2D) – Cohort 11a	**N=9**	**N=9**	**N=9**	**N=7**	**N=7**
Subjects with ≥1 CRS event	3 (33.3%)	3 (33.3%)	4 (44.4%)	**0**	**0**
Number of CRS events[a]	3	3	5	**0**	**0**
Grade 1	2 (66.7%)	2 (66.7%)	3 (60.0%)	**0**	**0**
Grade 2	1 (33.3%)	1 (33.3%)	2 (40.0%)	**0**	**0**
Priming/Intermediate/Full = 0.16/0.8/60 mg – Cohort 12	**N=3**	**N=3**	**N=3**	**N=3**	**N=3**
Subjects with ≥1 CRS event	**0**	**0**	2 (66.7%)	**0**	**0**
Number of CRS events[a]	**0**	**0**	2	**0**	**0**
Grade 1	**0**	**0**	1 (50.0%)	**0**	**0**
Grade 2	**0**	**0**	1 (50.0%)	**0**	**0**

* Note that starting from cohort 7 changes were made in the corticosteroid prophylaxis protocol.

Pharmacodynamics

Refer to section 2.10. Of note, In N=18 (28%) patients B-cells (identified based on CD19 expression) were detected (>10 cells/µL). In these patients epcoritamab induced rapid, sustained B-cell depletion at all doses tested.

2.6.5.2. Main study(ies)

GCT3013-01- A phase 1/2, open-label, dose-escalation trial of GEN3013 in patients with relapsed, progressive or refractory B-Cell lymphoma – aNHL cohort

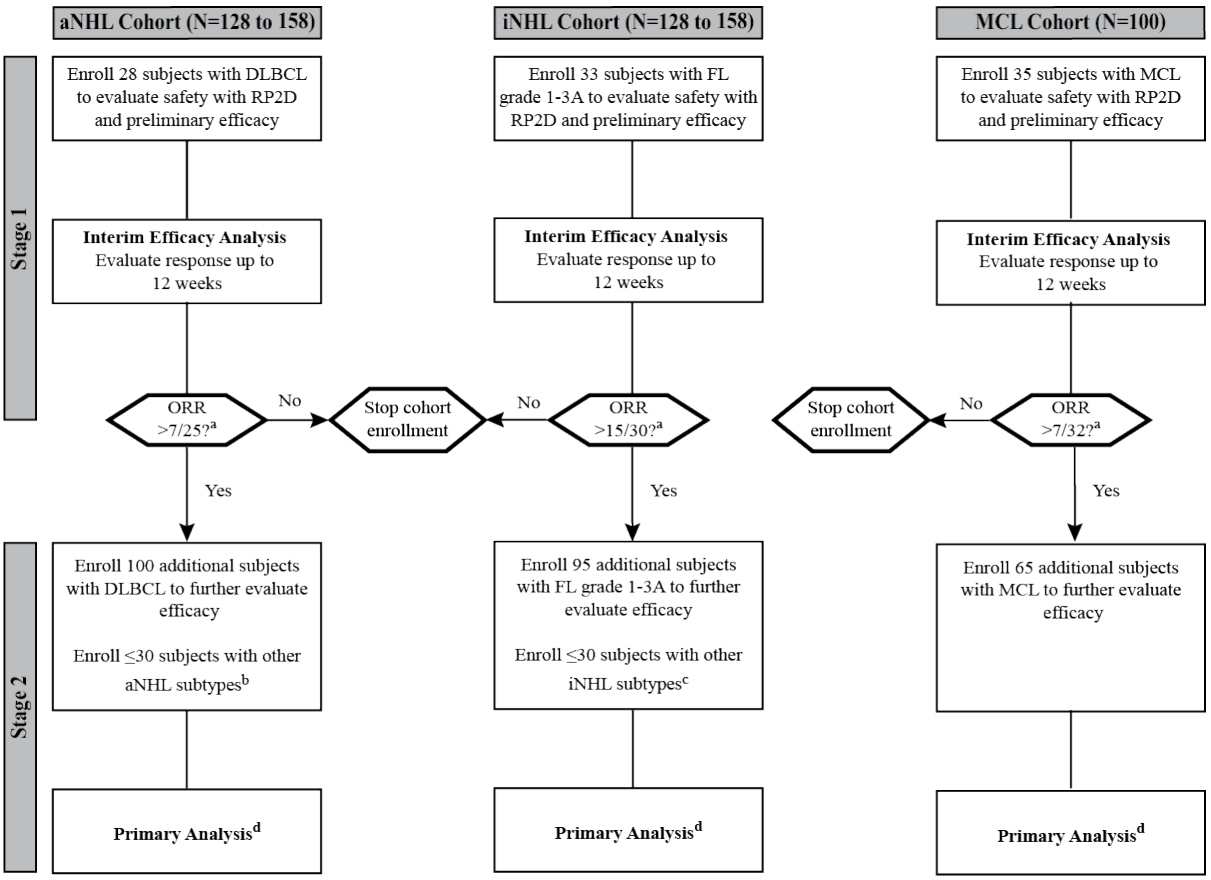
Methods

GCT3013-01 is an FIH, phase 1/2, multicenter, dose escalation/expansion, multi cohort, single arm trial in subjects aged 18 years or older who had relapsed, progressive and/or refractory mature B-cell lymphoma. The trial includes a Dose Escalation Part and an Expansion Part. The expansion part is considered to be the pivotal study by the applicant.

The aim of the Expansion Part of this trial was to evaluate the efficacy and safety of epcoritamab using the RP2D regimen in subjects with relapsed or refractory (R/R) aggressive NHL (aNHL), indolent NHL (iNHL), or MCL who had limited therapeutic options (Figure 10).

The Expansion Part was conducted in 2 stages for each cohort, as illustrated in Figure 12. In Stage 1, subjects with R/R DLBCL, FL grade 1-3A, and MCL were enrolled in each cohort and response data were collected. Following separate interim futility analyses in each cohort, conducted in the aNHL cohort when approximately 28 subjects had sufficient data (up to 12 weeks of follow up) to be evaluable for response, the protocol allowed additional subjects with aNHL, iNHL, or MCL to be enrolled for Stage 2 of each cohort to reach the required sample size for statistical analysis. In the aNHL expansion cohort, additional subjects with DLBCL were enrolled to reach a total of 139 subjects with DLBCL in this cohort. In addition, subjects with other types of LBCL (i.e., HGBCL, PMBCL, and FL 3B) were enrolled.

Figure 8: GCT3013-01 Expansion Scheme



aNHL = aggressive B-cell non-Hodgkin lymphoma; DLBCL = diffuse large B-cell lymphoma; FL = follicular lymphoma; iNHL = indolent non-Hodgkin lymphoma; MCL = mantle cell lymphoma; ORR = overall response rate; RP2D = recommended phase 2 dose.

- For the interim analysis, response was determined by Lugano criteria and assessed by the investigator and sponsor based on available data (eg, efficacy, safety, pharmacodynamics, biomarkers). The denominator for the interim analysis accounted for a 10% dropout rate.
- Other LBCL subtypes include high grade B-cell lymphoma, primary mediastinal B-cell lymphoma, and FL grade 3B.
- Other iNHL subtypes include marginal zone lymphoma and small lymphocytic lymphoma.
- For primary analysis, response was determined by Lugano criteria and assessed by IRC.

- **Study Participants**

The **main inclusion criteria** were:

I. Documented CD20+ mature B-cell neoplasm according to WHO classification Swerdlow et al., 2016 (Swerdlow et al., 2016) or WHO classification 2008 based on representative pathology report

A. Diffuse large B-cell lymphoma (de novo or transformed from all indolent subtypes including Richter's transformation), including:

1. Patients with "double-hit" or "triple-hit" DLBCL (technically classified in WHO 2016 as HGBCL, with MYC and BCL2 and/or BCL6 translocations). Note: Other double-/triple-hit lymphomas are not eligible

B. Other aggressive B-NHL (beginning in Stage 2):

1. Primary mediastinal (thymic) large B-cell lymphoma (PMBCL)

2. High-grade B-cell lymphoma (HGBL)
3. Follicular lymphoma grade 3B (FL3B)

C. Relapsed or refractory disease and previously treated with at least 2 lines of systemic antineoplastic therapy including at least 1 anti-CD20 monoclonal antibody containing therapy.

Note: Relapsed disease is defined as disease that has recurred ≥6 months after completion of therapy. Refractory disease is defined as disease that either progressed during therapy or progressed within 6 months (<6 months) of completion of therapy.

II. Either failed prior autologous hematopoietic stem cell transplantation (HSCT), or ineligible for autologous HSCT due to age, ECOG performance status, comorbidities, and/or insufficient response to prior treatment

III. Subjects must have had measurable disease (defined as a CT/MRI scan with involvement of 2 or more clearly demarcated lesions/nodes with a long axis >1.5 cm and short axis >1.0 cm or 1 clearly demarcated lesion/node with a long axis >2.0 cm and short axis ≥1.0 cm) and an FDG-PET scan that demonstrated positive lesion(s) (for FDG avid lymphomas only).

In addition patients needed to have an ECOG performance status 0, 1, or 2, adequate blood values, to be at least 4 weeks/ 5 half-lives (whichever is shorter except any anti-CD20 mAb or BTKi) from last dose of non-investigational systemic chemotherapy or antineoplastic agents, except for prior chimeric antigen receptor T-cell (CAR-T) therapy from which 30 days must pass prior to first GEN3013 administration. Patients also had to have lymphocyte counts $<5\times10^9$/L (for MCL: $<50\times10^9$/L).

The **main exclusion criteria** were:

- Primary central nervous system (CNS) lymphoma or CNS involvement by lymphoma at screening as confirmed by mandatory MRI/CT scan (brain) and, if clinically indicated, by lumbar puncture.
- Known past or current malignancy other than inclusion diagnosis, except for:
    - Cervical carcinoma of Stage 1B or less.
    - Non-invasive basal cell or squamous cell skin carcinoma.
    - Non-invasive, superficial bladder cancer.
    - Prostate cancer with a current PSA level <0.1 ng/mL.
        - Any curable cancer with a complete response (CR) of >2 years duration
- AST, and/or ALT >3x upper limit of normal, total bilirubin >1.5x upper limit of normal, unless bilirubin rise is due to Gilbert's, syndrome or of non-hepatic origin, Estimated GFR <45 mL/min/1.73m2
- Any prior therapy with an investigational bispecific antibody targeting CD3 and CD20
- Eligible for curative intensive salvage therapy followed by high dose chemotherapy with HSCT rescue
- Autologous HSCT within 100 days prior to first GEN3013 administration, or any prior allogeneic HSCT or solid organ transplantation

Comorbidities such as active hepatitis B or ongoing hepatitis C infection, known HIV infection, seizure disorder requiring therapy, chronic ongoing infectious diseases (or 2 weeks prior to the first dose of GEN3013), known clinically significant cardiac disease, auto-immune disease requiring permanent immunosuppression, or a contraindication to all uric acid lowering agents.

- **Treatments**

Epcoritamab was administered by SC injection in treatment cycles of 4 weeks, ie, 28 days. A priming dose of 0.16 mg (C1D1), an intermediate dose of 0.8 mg (C1D8), and a full dose of 48 mg (C1D15, C1D22, and thereafter), was administered according to the following schedule:

- Cycles 1 to 3: Days 1, 8, 15, and 22 (QW)
- Cycles 4 to 9: Days 1 and 15 (Q2W)
- Cycle 10 and beyond until unacceptable toxicity, PD, or withdrawal of consent: Day 1 (Q4W)

During the Expansion Part, hospitalization was only required for a minimum of 24 hours after the first full dose of epcoritamab in C1.

Subject's treatment was to be discontinued if they had an unacceptable AE, became pregnant, withdrew consent, or if the investigator or sponsor believed discontinuation was in the best interest of the subject (eg, in case of AEs) or trial (eg, in case of eligibility criteria violation or noncompliance with the protocol). Treatment discontinuation was also intended if the subject experienced clinical progression or disease progression after factoring in LYRIC for assessment of indeterminate response (Cheson et al., 2016).

During clinical development, the manufacturing processes of the 3001d and 3005a biological intermediates, epcoritamab drug substance and drug product were transferred to new manufacturing sites to support commercial manufacturing. The manufacturing processes were further developed and scaled up. The commercial product was introduced during the conduct of the Expansion Part of the GCT3013-01 and GCT3013-04 trials during re-supply; therefore, some subjects have received epcoritamab drug product manufactured with the 2 different processes.

Medication Prior to Epcoritamab Administration

Subjects were premedicated 30 to 120 minutes prior to the first 4 doses of epcoritamab with the following in Cycle 1:

- Prednisolone (100 mg oral or IV) or equivalent on D1-D4, D8-D11, D15-18 and D22-D25.
- Diphenhydramine (50 mg oral or IV) or equivalent and Acetaminophen (650 to 1000 mg oral) on D1, D8, D15 and D22

For subsequent doses of epcoritamab, premedication and CRS prophylaxis were optional. With regard to corticosteroids if CRS≥ Grade 2 occurred following the 4th epcoritamab administration, the 4 day consecutive corticosteroids must also be repeated for CRS prophylaxis with each epcoritamab dose until 1 full epcoritamab dose is administered without subsequent occurrence of if CRS≥ Grade 2.

Concomitant Therapy

For treatment of CRS, subjects were recommended to receive supportive care, including infusion of saline, systemic glucocorticosteroids, antihistamines, antipyretics, support for blood pressure (vasopressin, vasopressors), support for low-flow and high-flow oxygen and positive pressure ventilation and/or mAbs against IL-6R (eg, intravenous administration of tocilizumab).

Subjects considered to have an increased risk for CTLS were recommended to receive hydration and prophylactic treatment with a uric acid lowering agent. If signs of CTLS occurred, supportive therapy, including rasburicase, was allowed. The use of growth factors for neutropenia such as granulocyte colony stimulating factor was allowed during treatment with epcoritamab. In case of recurring ≥ grade 3 neutropenia, use of growth factors was mandated. Prophylactic antibiotic, antiviral and antifungal therapies were allowed. For patients who are considered to have an increased risk for herpes and/or pneumocystis jiroveci infections, prophylaxis is recommended, unless medically contraindicated. For patients who are considered to have an increased risk for other infections, prophylactic therapy is recommended, unless medically contraindicated.

- **Objectives**

The primary objective was to evaluate clinical efficacy as determined by Lugano criteria.

Secondary objectives were:

- To further evaluate clinical efficacy as determined by Lugano criteria
- To evaluate the clinical efficacy as determined by LYRIC
- To evaluate MRD status as a clinical efficacy endpoint
- To evaluate safety and tolerability of epcoritamab
- To evaluate the PK and immunogenicity of epcoritamab
- To evaluate PROs related to lymphoma symptoms

To evaluate PROs related to well-being and general health status

- **Outcomes/endpoints**

The primary endpoint is:

- ORR determined by Lugano criteria as assessed by independent review committee (IRC)

Secondary endpoints are:

- DOR determined by Lugano criteria as assessed by IRC
- CR rate determined by Lugano criteria as assessed by IRC
- Duration of complete response (DOCR) by Lugano criteria as assessed by IRC
- PFS determined by Lugano criteria as assessed by IRC
- Time to response (TTR) determined by Lugano criteria as assessed by IRC
- ORR, CR, PFS, DOR, DOCR, TTR determined by LYRIC as assessed by IRC
- OS
- TTNT
- Rate of Minimal residual disease (MRD) negativity
- Safety, PK parameters and changes in lymphoma symptoms as measured by the FACT-Lym

Efficacy assessments were conducted as specified in the visit assessment schedule and included the following: scheduled imaging assessments during Weeks 6, 12, 18, 24, 36, 48, and then every 24 weeks thereafter, physical examination (including constitutional symptoms), ECOG performance status, MRD status, and other procedures as necessary.

- **Sample size**

The Expansion Part of the trial was carried out within 3 cohorts in a 2-stage design. In the aNHL expansion cohort, 28 subjects with DLBCL were enrolled in Stage 1. The interim analysis for the aNHL cohort was based on ORR as assessed by the investigator and was to be conducted when approximately 25 patients with DLBCL had sufficient data (up to 12 weeks of follow-up) to be evaluable for response. If the futility criteria were met (no more than 7 responders out of 25 response evaluable subjects with up to 12 weeks of follow up), no further expansion was planned. Based on results from the interim futility analysis, an additional 100 subjects with DLBCL were to be enrolled to Stage 2, along with up to 30 subjects with other types of aNHL (HGBCL, PMBCL, and FL3B). In total, up to 158 subjects were to be enrolled in the aNHL expansion cohort.

Assuming a non-evaluable rate of 10%, a sample size of 128 subjects in DLBCL group was estimated to provide approximately 90% power to detect the alternative hypothesis of at least 50% ORR while ensuring a 2-sided significance level of 0.05 using one-sample exact binomial test under the null hypothesis of at most 35% ORR. The probability of futility at the end of Stage 1 was approximately 30% under the null and 2.1% under the alternative hypothesis

- **Randomisation and Blinding (masking)**

N/A

- **Statistical methods**

Analysis Populations

The analysis sets for the Expansion Part were as follows:

- Enrolled subjects: All subjects who signed the informed consent form.
- FAS: All subjects who received at least 1 dose of epcoritamab. All efficacy analyses were performed on the FAS.
- SAF: All subjects who received at least 1 dose of epcoritamab (same as FAS). All safety analyses were performed on the SAF.
- RES: All subjects in the FAS with measurable disease at baseline, and either at least 1 postbaseline disease evaluation or had died within 60 days of first dose without postbaseline disease assessment.
- mRES: All subjects in the RES who had received at least 1 full dose of epcoritamab.
- PP Analysis Set: All subjects in the FAS with measurable disease at baseline and no important protocol deviations.
- PK Analysis Set: All subjects in the FAS with at least 1 PK sample collected, and sufficient data to calculate at least 1 plasma PK parameter for epcoritamab.
- IAS: All subjects in the FAS with an evaluable baseline ADA sample, and at least 1 evaluable on-treatment ADA sample.
- MRD-Evaluable Set: All subjects in the FAS who had at least 1 baseline or on treatment MRD sample and were either MRD positive or not evaluated at baseline.
- PRO Analysis Set: All subjects in the FAS with a baseline and at least 1 postbaseline PRO score.
- FISH Analysis Set: All subjects in the FAS with available screening tumor tissue evaluable for MYC.

Efficacy Analyses

Primary endpoint analyses

Primary analysis for the Expansion Part of this trial was based on IRC-assessed ORR determined by Lugano criteria in the FAS. ORR is defined as proportion of subjects who achieved Best Overall Response (BOR) of complete response or partial response in an analysis set. The BOR prior to initiation of subsequent anti-lymphoma therapy per response criteria was summarized. Number and frequency of BOR was presented for response categories per Lugano criteria (Cheson et al., 2014). The ORR, disease control rate (BOR of SD and better) and the corresponding 95% exact CI were provided for subjects with DLBCL, other LBCL subtypes, and LBCL. Sensitivity analyses of ORR were performed in a similar manner as the primary analysis for the following.

- IRC-assessed ORR per Lugano criteria in the PP, RES, and mRES
- IRC-assessed CT-based ORR per Lugano criteria in the FAS and RES
- Investigator-assessed ORR per Lugano criteria in the FAS, PP, RES, and mRES

Supplemental analyses included subgroup analysis of ORR and concordance between IRC- and investigator-assessed BOR based on Lugano criteria in the FAS.

Secondary endpoints

Key secondary endpoint of IRC-assessed ORR by LYRIC were provided in the FAS along with corresponding 95% exact CI. Additional response category by LYRIC included indeterminate response

(IR). Sensitivity analyses for IRC-assessed ORR by LYRIC were conducted for RES population. Similar analyses were also performed for investigator assessed ORR by LYRIC in the FAS. CR rate analyses will be performed with a similar manner as ORR.

TTR and DOR will be derived for subjects who achieved BOR of PR or CR. TTR is defined as the time from Day 1 of Cycle 1 to first documentation of objective tumor response (PR or better). DOR is defined as the time from the first documentation of response (CR or PR) to the date of PD or death, whichever occurs earlier. Date of PD is defined as the earliest date of documented progression after which there is no more PR or CR assessment. The DOR will be estimated using the Kaplan-Meier (KM) product-limit method. Similar analysis methods will be used for TTCR and DOCR. DoCR is defined as the time from the first documentation of CR to the date of PD or death, whichever occurs earlier. DoCR will be derived for subjects reaching CR.

PFS is defined as the time from Day 1 of Cycle 1 to the date of PD or death due to any cause, whichever occurs earlier. Date of PD is defined as the earliest date of documented progression after which there is no more PR or CR assessment. PFS will be derived for all subjects and analyzed using similar methods as DOR. The duration of disease follow-up, defined as the time between Day 1 of Cycle 1 to the date of PD or death due to any cause, whichever occurs earlier, will be calculated based on reverse Kaplan-Meier method.

Clinical progression without documented radiographical progression per Lugano or LYRIC criteria will not be considered progression for determination of PFS. Main analysis of PFS will be based on IRC disease assessment per Lugano and LYRIC criteria using primary definition in the FAS. Similar analyses based on investigator disease assessment in the FAS will also be conducted.

OS is defined as the time from Day 1 of Cycle 1 to death from any cause. If a patient is not known to have died, then OS will be censored at the latest date the patient was known to be alive. Survival status will be assessed at least every 3 months after last administration of epocoritamab and continues until the patient dies or withdraws from the trial. OS will be derived for all subjects and analyzed in the FAS using similar methods as DOR.

TTNT is defined as the time from Day 1 of Cycle 1 to first recorded administration of subsequent anti-lymphoma therapy with curative intent or death, whichever occurs earlier. Subjects died due to disease progression will be considered an event. Death due to other reasons will be censored at the death date. The subsequent anti-lymphoma therapies for TTNT events will in general consist of systemic anti-lymphoma therapy, and curative intent radiotherapy for one and only target lesion. The exception is censoring subject without disease progression while receiving subsequent stem cell transplant after responding to epcoritamab to be consistent with the intent to measure duration of clinical benefit using TTNT. Subjects alive and without initiation of subsequent anti-lymphoma therapy will be censored at the last known alive date. TTNT will be derived for all subjects and analyzed in the FAS using similar methods as DOR.

MRD negativity in PBMCs is defined as less than 1 tumour clone in 10^{-6} leukocytes at any on-treatment time point. MRD assessment in ctDNA (i.e., plasma) was also done (MRD negative defined as the absence of any detectable clone sequence per ml volume at any on-treatment time point). For evaluation of MRD negativity rate, subjects are considered MRD negative if there is at least one on-treatment MRD negative whole blood sample; all remaining subjects in the FAS are considered MRD positive (e.g. those who only have MRD positive test results or those who have no MRD assessment data). Duration of MRD negativity is defined as the number of days from the first documentation of MRD- to the date of MRD status change (not MRD-). The primary MRD- threshold is selected as of 10-5. Other thresholds, including 10-4 and 10-6, may also be explored.

Exploratory analysis of MRD negativity will also be performed in plasma (ctDNA) samples. MRD-threshold will be determined by the limit of detection (LOD) of ctDNA in the sample and may be reported as either MRD-, MRD+ or not determined for samples that did not pass preanalytical QC by the vendor. For evaluation of MRD negativity rate, subjects are considered MRD negative if there is at least one on-treatment MRD negative plasma sample; all remaining subjects in the FAS are considered MRD positive.

MRD- rate analyses will be performed in the FAS with a similar manner as ORR, and duration of MRD- analyses will be conducted in similar methods for DOR.

Descriptive statistics for FACT-Lym and EQ-5D-3L assessment along with changes from baseline at each assessment time point will be presented for FACT-Lym TOI, FACT-G total score, FACT-Lym total scores, subscale scores, and 6-items of special interest and EQ-5D-3L. A line graph summarizing the mean change from baseline with standard error bar, with a reference line on the MID will also be produced for FACT-Lym TOI, FACT-G total score, FACT-Lym total scores, FACT-LymS and EQ-5D-3L. A change from baseline of 11 for the FACT-Lym TOI, of 7 for the FACT-G total score, of 11.2 for the FACT-Lym total scores, and of 5.4 for the FACT-LymS are considered minimally importance difference (MID) (Webster et. al., 2003). A change from baseline of 0.08 for the EQ- 5D-3L utility index score and of 7 for the EQ VAS are considered MID for the EQ-5D-3L (Pickard AS, et. al., 2007).

Exploratory endpoints

All biomarker assessments will be performed at a central laboratory. Biomarker assessments that are intended to evaluate potential pharmacodynamic markers and to identify markers predictive of response or resistance to GEN3013 are exploratory in nature.

ORR, CR rate based on IRC-assessment per Lugano criteria in the FAS will be summarized within subgroups listed along with 95% exact CI in a forest plot for DLBCL and aNHL. In the case a subgroup includes less than 20 subjects, the analysis for the given subgroup will not be carried out or combining subgroups may be considered. The following analyses have been prespecified: Age (<65 years, 65 to <75 years, ≥75 years); Gender (male, female); Race (White, Asian, Black, or Other); Region (North America, Europe, other); Baseline ECOG performance score (0, 1, 2 or plus); Baseline weight (< 65 kg, 65 to < 85 kg, ≥ 85 kg); Number of prior anti-lymphoma therapies (2, 3, 4+); Time from last anti-CD20 therapy till first dose of GEN3013 (<median, ≥median); Prior CAR-T experience (yes, no); Prior ASCT (yes, no); Prior anti-lymphoma therapy status (primary refractory, other); Most recent prior anti-CD20 containing therapy (refractory, relapse); Chromosomal abnormality (double-hit, triple-hit, other); Ann Arbor staging (I/II, III/IV); IPI (0-2, ≥3); DLBCL disease state (De novo, transformed); Molecular classification (GCB, non-GCB); Molecular classification (ABC); Overall presence of ADAs (Positive/Non-Positive).

Results

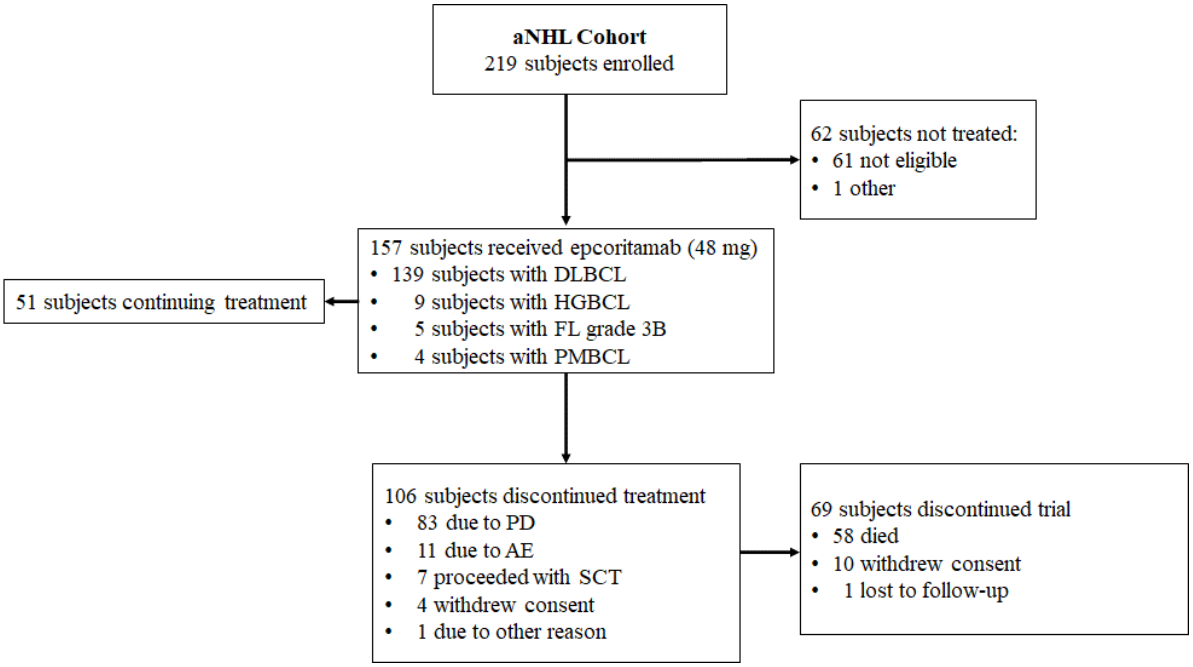
- **Participant flow**

As of the data cutoff date of 31 Jan 2022, a total of 219 subjects were screened and 157 subjects received at least one dose of epcoritamab in the aNHL expansion cohort. A diagram showing the disposition of the 219 subjects screened in the aNHL expansion cohort is provided in Figure 15.

In total, 62 (28.3%) subjects enrolled (i.e. signed the informed consent form) in the study, but were not treated with epcoritamab. These were considered screen failures as the primary reason for not being treated was due to ineligibility in 61 subjects and for an otherwise uncategorised reason (bridging therapy prior to CAR T-cell therapy) in 1 subject. The latter was an error. This subject was on

Day 26 of washout from previous antineoplastic therapy (post treatment) at the time of screening and therefore did not meet the inclusion criteria.

Figure 9: Subject Disposition – aNHL Cohort, Expansion Part



Abbreviations: AE = adverse event; aNHL = aggressive B-cell non-Hodgkin lymphoma; DLBCL = diffuse large B-cell lymphoma; HGBCL = high-grade B-cell lymphoma, FL = follicular lymphoma; PD = progressive disease; PMBCL = primary mediastinal B-cell lymphoma; SCT = stem cell transplant.
Data cutoff date: 31 Jan 2022

Table 13: Disposition of Subjects – aNHL Cohort, Expansion Part (Full Analysis Set)

Number of Treated Subjects, n (%)	**aNHL Cohort**		
	DLBCL (N=139)	Other Subtypes[a] (N=18)	LBCL (N=157)
Ongoing study treatment	47 (33.8%)	4 (22.2%)	51 (32.5%)
Discontinued study treatment	92 (66.2%)	14 (77.8%)	106 (67.5%)
Primary reason for treatment discontinuation			
Progressive disease[b]	72 (51.8%)	11 (61.1%)	83 (52.9%)
Clinical progression	12 (8.6%)	2 (11.1%)	14 (8.9%)
Disease progression according to response criteria	60 (43.2%)	9 (50.0%)	69 (43.9%)
Adverse event	11 (7.9%)	0	11 (7.0%)
Death	0	0	0
Withdrawal by subject	3 (2.2%)	1 (5.6%)	4 (2.5%)
Decision to proceed with transplant	5 (3.6%)	2 (11.1%)	7 (4.5%)

Number of Treated Subjects, n (%)	**aNHL Cohort**		
	DLBCL (N=139)	Other Subtypes[a] (N=18)	LBCL (N=157)
Other[c]	1 (0.7%)	0	1 (0.6%)
Subjects remain on trial	76 (54.7%)	12 (66.7%)	88 (56.1%)
Discontinued from trial	63 (45.3%)	6 (33.3%)	69 (43.9%)
Death	53 (38.1%)	5 (27.8%)	58 (36.9%)
Lost to follow up	1 (0.7%)	0	1 (0.6%)
Subject withdrew consent from trial	9 (6.5%)	1 (5.6%)	10 (6.4%)

Abbreviations: aNHL = aggressive B-cell non-Hodgkin lymphoma; DLBCL = diffuse large B-cell lymphoma; HGBCL = high-grade B-cell lymphoma; LBCL = large B-cell lymphoma

a Other includes 9 subjects with HGBCL, 5 subjects with follicular lymphoma (FL) grade 3B and 4 subjects with primary mediastinal B-cell lymphoma (PMBCL).

b Progressive disease includes both clinical progression and documented radiographic disease progression.

c One subject discontinued treatment following a partial response on epcoritamab to proceed to chimeric antigen receptor T cell therapy.

Data cutoff date: 31 Jan 2022

- **Recruitment**

The Expansion Part of the trial began on 19 Jun 2020 (first subject signed informed consent) and clinical data cut-off date was 31 Jan 2022. The trial is ongoing and the date of last observation for last subject recorded as part of the database for this analysis has not yet been reached.

- **Conduct of the study**

As of the data cut-off date of 31 Jan 2022, 7 protocol amendments were made to the original protocol Version 2.0 (dated 15 Nov 2017). The original protocol version 1.0 was dated 09 Nov 2017 but was not submitted. A summary of key changes with each amendment is provided in Table 27.

Table 14: Summary of protocol amendments

Amendment number and version number	**Issue date**	**Key changes**
Amendment 1-4; version 3.0-6.0	18 Jan 2018 – 21 Jun 2019	Not applicable to the Expansion Part of the trial. Amendments were made on the design, dose-levels and escalation steps, exclusion criteria, CRS management, management of pseudo progression for the escalation part.
Amendment 5; Version 7.0	4 Nov 2019	Amendment 5 was prepared to provide details regarding the Expansion Part of the trial. Rationale, trial design, objectives/endpoints, inclusion/exclusion criteria, dose schedule and administration, objectives/endpoints, statistical analysis (including sample size), safety and other relevant sections in the protocol were updated to include information for the Expansion Part. Definition of end-of-trial was updated. Clarified that, in the Dose Escalation Part of the trial, dose escalation could continue as planned with the Modified Bayesian optimal interval design if a maximum tolerated dose was not reached. Clarifications on the end of treatment visit and safety follow-up visit were separate visits. Clarified that, in addition to prior cancer therapy, prior cancer surgery, radiotherapy, chemo-radiation, systemic treatment regimens, etc. from the time of diagnosis until enrollment in this trial were to be reported in the appropriate section of the eCRF at screening.
Amendment 6;	8 Jun 2020	In response to Health Authority feedback, the safety reporting period after last dose of

Version 8.0		epcoritamab was increased to 60 days for the Expansion Part of the trial. Inclusion and exclusion criteria were revised for the Expansion Part of the trial for clarity (it was specified that patients needed to have R/R disease) based on Health Authority feedback. Based on the assessment of the CRS incidence in the Dose Escalation Part of the ongoing trial, the steroid prophylaxis period was increased from 3 consecutive days to 4 consecutive days (Days 1 to 4) for the first 4 doses of epcoritamab For the Expansion Part, a bone marrow biopsy was mandated at screening to assess bone marrow involvement. Rationale for the R2PD to be used in the Expansion Part was added. Qualitative interviews (PRO assessment) were added to the PROs in the Expansion Part.
Amendment 7; Version 9.0	23 Sep 2020	A cohort of subjects with MCL was added to the Expansion Part of the trial. As a result, the trial design was updated in relation to the MCL cohort. The inclusion criteria were amended to include a definition of relapsed and refractory disease. Other key changes made to the protocol were: Added 'duration of CR (DOCR)' to the secondary endpoints to support the objective of: "To further evaluate clinical efficacy as determined by Lugano criteria." Added 'CR rate determined by LYRIC as assessed by IRC' and 'DOCR determined by LYRIC as assessed by IRC' to the secondary endpoints to support the objective of: "To evaluate the clinical efficacy as determined by LYRIC". The endpoint of 'MRD status by detection of cancer cell gene sequences' was changed to 'rate of MRD negativity'. Dose modification (dose delay and discontinuation) criteria for the Expansion Part were updated to incorporate findings from the ongoing trial. Added appendix for grading and management of ICANS.

Abbreviations: CR = complete response; DOCR = duration of complete response; eCRF = electronic case report form; ICANS = immune effector cell-associated neurotoxicity syndrome; IRC = Independent Review Committee; LYRIC = Lymphoma Response to Immunomodulatory Therapy Criteria; MCL = mantle cell lymphoma; MRD = minimal residual disease; PRO = patient-reported outcome; RP2D = recommended phase 2 dose.

Changes to the Planned Statistical Analyses - Forest plots were not produced for PFS or OS. Instead, results for the subgroup analysis of PFS and OS were presented in table format for this single-arm aNHL expansion cohort. Due to missing baseline tumor biopsies, subject consent preference, and/or unevaluable assay results, all exploratory MRD analyses were performed using the MRD-evaluable subset, which included subjects who had ≥1 baseline or on treatment MRD sample and were either MRD positive or not evaluated at baseline. A retrospective, central FISH analysis was performed on available diagnostic baseline tumor tissue sections to identify MYC, BCL2 and/or BCL6 rearrangements (i.e., HGBCL by FISH) with a consistent method. A FISH Analysis Set was defined for these analyses.

Protocol Deviations

A summary of all protocol deviations in the aNHL cohort (N = 157) of the GCT3013-01 trial expansion part grouped by deviation type is presented in Table 21 and important protocol deviations are summarized in Table 28. At least one important protocol deviation occurred in 6 (3.8%) subjects in the aNHL expansion cohort. None of the important protocol deviations were deemed to have had a meaningful impact on the interpretation of the trial results.

Table 21: All Protocol Deviations in GCT3013-01 Expansion Part - Subjects in aNHL Cohort - Full Analysis Set

	aNHL Cohort		
	DLBCL (N=139)	**Other (N=18)**	**LBCL (N=157)**
Number of Subjects with at least one protocol deviation	131 (94.2%)	18 (100%)	149 (94.9%)

	aNHL Cohort		
	DLBCL (N=139)	**Other (N=18)**	**LBCL (N=157)**
Laboratory	105 (75.5%)	12 (66.7%)	117 (74.5%)
Visit/Procedure required	101 (72.7%)	14 (77.8%)	115 (73.2%)
Visit Schedule	57 (41.0%)	8 (44.4%)	65 (41.4%)
Other[a]	47 (33.8%)	6 (33.3%)	53 (33.8%)
Dosing	34 (24.5%)	3 (16.7%)	37 (23.6%)
Regulatory or ICH-GCP	30 (21.6%)	1 (5.6%)	31 (19.7%)
Equipment or Facilities	28 (20.1%)	2 (11.1%)	30 (19.1%)
Study Procedure (not related to-subject)	23 (16.5%)	2 (11.1%)	25 (15.9%)
Informed Consent	19 (13.7%)	4 (22.2%)	23 (14.6%)
Training or Qualification	18 (12.9%)	2 (11.1%)	20 (12.7%)
Non-Compliance	14 (10.1%)	2 (11.1%)	16 (10.2%)
IP (not related to subject)	11 (7.9%)	3 (16.7%)	14 (8.9%)
Enrolment Criteria	9 (6.5%)	0	9 (5.7%)
Data Privacy	4 (2.9%)	1 (5.6%)	5 (3.2%)
Safety Reporting	4 (2.9%)	1 (5.6%)	5 (3.2%)
Regulatory	2 (1.4%)	0	2 (1.3%)

aNHL = aggressive non-Hodgkin lymphoma; a DLBCL = diffuse large B-cell lymphoma; ICH-GCP International Council for Harmonisation-Good Clinical Practice; IP = investigational product; LBCL = large B-cell lymphoma.

Note: Percentages calculated based on number of subjects in FAS.

a. Other protocol deviations included timing of procedures, timing of data reviews, discrepancies between source data and source files, and other minor deviations not categorized within the deviation types.

Table 15: Important Protocol Deviations – aNHL Cohort, Expansion Part (Full Analysis Set)

	aNHL Cohort		
	DLBCL (N=139)	Other Subtypes[a] (N=18)	LBCL (N=157)
Number of subjects with at ≥1 important protocol deviation	**6 (4.3%)**	**0**	**6 (3.8%)**

	aNHL Cohort		
	DLBCL (N=139)	Other Subtypes[a] (N=18)	LBCL (N=157)
Enrollment criteria	3 (2.2%)	0	3 (1.9%)
Dosing	2 (1.4%)	0	2 (1.3%)
Informed consent	1 (0.7%)	0	1 (0.6%)

Abbreviations: aNHL = aggressive B-cell non-Hodgkin lymphoma; DLBCL = diffuse large B-cell lymphoma; LBCL = large B cell lymphoma.
a Other includes 9 subjects with high grade B-cell lymphoma (HGBCL), 5 subjects with follicular lymphoma (FL) grade 3B and 4 subjects with primary mediastinal B-cell lymphoma (PMBCL).
Data cutoff date: 31 Jan 2022
Source: Table 14.1.1.4.1

Important protocol deviations included the following:

- Enrollment criteria (3 subjects):
  - Subject who did not meet inclusion criterion No. 6, local laboratories pre-C1D1 platelet level was 47 × 10^9/L, under the required level of 50 × 10^9/L, and also did not meet inclusion criterion No. 7, local laboratories pre-C1D1 neutrophil level was 0.5 × 10^9/L, under the required level of ≥1.0 × 10^9
  - Subject's CR for clear cell renal cell carcinoma was maintained <2 years prior to first dose, a violation of exclusion criterion No. 21 in the Expansion Part of the trial
  - Subject had received prior allogeneic HSCT.
- Dosing (2 subjects):
  - Prophylactic medication administered 3 days instead of 4 days for C1D1
  - Mandatory prophylactic corticosteroids were not administered at C1D17

Informed consent: subject was incorrectly consented to the wrong trial (a different trial with epcoritamab being conducted at the same site); however, the correct informed consent form was signed prior to study drug administration.

A request for a routine GCP inspection has been adopted for the escalation part of the GCT3013-01 study. Overall it is the recommendation of the inspectors that the data of the escalation part of the GCT3013-01 clinical trial can be used for evaluation and assessment of the application (EMA/IN/0000118168).

In general the conduct of the escalation part of the GCT3013-01 clinical trial was not fully ICH-GCP compliant, based on the critical and major deviations mentioned in the integrated inspection report. The observed findings, however, were unlikely to have a significant impact on data integrity within the inspected escalation part of the GCT3013-01 clinical trial according to the inspectors. The inspection team did not identify any restrictions on the usability of the reported trial data. The escalation part of GCT3013-01 clinical trial is still considered to be conducted within internationally accepted ethical standards. Although critical and major findings were reported that could have affected the integrity of the collected and reported data, the inspectors consider the data of the escalation part of the GCT3013-01 clinical trial, as reported in the corresponding CSR, to be acceptable. The responses to the inspection report including the timely implementations of the actions for ongoing (if applicable) and future clinical studies, as set out in the CAPA plan, will further enhance the quality of clinical trials performed by Genmab.

- **Baseline data**

Table 29 presents a summary of key demographic information and disease characteristics for subjects in the aNHL expansion cohort.

Table 16: Key Demographic and Disease Characteristics – aNHL Cohort, Expansion Part (Full Analysis Set)

Number of Treated Subjects, n (%)	**aNHL Cohort**		
	DLBCL (N=139)	Other Subtypes (N=18)	LBCL (N=157)
Age (years)			
Median (range: min: max)	66.0 (22, 83)	55.5 (20, 74)	64.0 (20, 83)
Age category (years)			
<65 years	66 (47.5%)	14 (77.8%)	80 (51.0%)
65 to <75 years	44 (31.7%)	4 (22.2%)	48 (30.6%)
≥75 years	29 (20.9%)	0	29 (18.5%)
Sex (at birth)			
Male	85 (61.2%)	9 (50.0%)	94 (59.9%)
Female	54 (38.8%)	9 (50.0%)	63 (40.1%)
Race			
White	84 (60.4%)	12 (66.7%)	96 (61.1%)
Asian	27 (19.4%)	3 (16.7%)	30 (19.1%)
Other	5 (3.6%)	2 (11.1%)	7 (4.5%)
Not reported[a]	23 (16.5%)	1 (5.6%)	24 (15.3%)
ECOG performance status			
0	67 (48.2%)	7 (38.9%)	74 (47.1%)
1	67 (48.2%)	11 (61.1%)	78 (49.7%)
2	5 (3.6%)	0	5 (3.2%)

Number of treated subjects, n (%)	**aNHL Cohort**		
	DLBCL (N=139)	Other Subtypes (N=18)	LBCL (N=157)
Disease type at trial entry			
DLBCL	139 (100%)	0	139 (88.5%)
HGBCL	0	9 (50.0%)	9 (5.7%)
PMBCL	0	4 (22.2%)	4 (2.5%)
FL grade 3B	0	5 (27.8%)	5 (3.2%)
DLBCL type			
De novo	97 (69.8%)	-	97 (61.8%)
Transformed	40 (28.8%)	-	40 (25.5%)
DLBCL cell of origin classification per local laboratory[b]			
GCB	65 (46.8%)	0	65 (41.4%)
ABC/non-GCB	56 (40.3%)	0	56 (35.7%)
Unknown	18 (12.9%)	0	18 (11.5%)
Not applicable	0	18 (100%)	18 (11.5%)
Median time from initial diagnosis to first dose[c] (min, max), yrs[d]	1.6 (0.0, 28.4)	1.9 (0.4, 8.2)	1.6 (0.0, 28.4)
MYC and BCL2 and/or BCL6 rearrangements per central laboratory FISH analysis			
Number evaluated	88	11	99
Double-hit lymphoma	11 (12.5%)	1 (9.1%)	12 (12.1%)
Triple-hit lymphoma	1 (1.1%)	0	1 (1.0%)
Other	76 (86.4%)	10 (90.9%)	86 (86.9%)
IPI (at study entry)			
0-2	55 (39.6%)	0	55 (35.0%)
≥3	82 (59.0%)	0	82 (52.2%)

Number of treated subjects, n (%)	aNHL Cohort		
	DLBCL (N=139)	Other Subtypes (N=18)	LBCL (N=157)
Unknown	2 (1.4%)	0	2 (1.3%)
Not applicable	0	18 (100%)	18 (11.5%)
Median number (min, max) of prior lines of anti-lymphoma therapy	3.0 (2, 11)	4.0 (2, 5)	3.0 (2, 11)
1	0	0	0
2	41 (29.5%)	5 (27.8%)	46 (29.3%)
3	47 (33.8%)	3 (16.7%)	50 (31.8%)
≥4	51 (36.7%)	10 (55.6%)	61 (38.9%)
Median time (min, max) from end of last-line anti-lymphoma therapy to first dose of epcoritamab (months)	2.5 (0, 153)	2.4 (1, 17)	2.4 (0, 153)

Abbreviations: ABC = activated B-cell; aNHL = aggressive B-cell non-Hodgkin lymphoma; CrCl = creatinine clearance; DLBCL = diffuse large B-cell lymphoma; ECOG = Eastern Cooperative Oncology Group; FL = follicular lymphoma; GCB = germinal center B-cell; HGBCL = high-grade B-cell lymphoma; IPI = International Prognostic Index; LBCL = large B-cell lymphoma; max = maximum; min = minimum; NCI = National Cancer Institute; min = minimum; MZL = marginal zone lymphoma; PMBCL = primary mediastinal large B-cell lymphoma; SLL = small lymphocytic lymphoma.

a Not reported in non-US countries

b Subjects who had results from local laboratory analysis collected as medical history.

c Time from diagnosis of disease recorded at time of trial entry

d Two patients who transformed from FL to DLBCL had 0.02 and 0.04 years, respectively, from the time of diagnosis of DLBCL to first dose of epcoritamab.

Data cutoff date: 31 Jan 2022
Source: Table 14.1.1.2, Table 14.1.1.3, Table 14.1.1.3.1 and Table 14.1.1.6.1.

A normal baseline renal function was observed in 67 (42.7%) patients in the aNHL cohort, 63 (40.1%) patients had a mildly impaired renal function. In total 24 (15.3%) subjects (had moderately impaired renal function and no subjects had severely impaired renal function. These numbers were 57 (41.0%), 59 (42.4%) and 21 (15.1%) and 0 in DLBCL patients.

Baseline hepatic function was normal in 122 (77.7%) of the patients in the aNHL cohort, mild dysfunction was seen in 30 (19.1%) of the patients and moderate dysfunction in 1 (0.6%) patient. In DLBCL patients these numbers were 109 (78.4%); 26 (18.7%) and 1 (0.7%) respectively. Baseline renal function calculated based on estimate creatine clearance using the Cockcroft Gault method.

Approximately two-thirds of patients with LBCL (97 [61.8%] subjects) had Ann Arbor stage IV lymphomas and 21 (13.3%) had Ann Arbor stage III (in DLBCL patients 86 (61.9%) and 18 (12.9%) respectively).

Prior anti-lymphoma therapies

The number of prior cancer therapies for subjects in the aNHL expansion cohort are summarized in Table ***30***. A total of 31 (19.7%) subjects with LBCL had a prior ASCT. One subject had received a prior allogeneic HSCT, which was identified as an important protocol deviation. Of the 31 (19.7%) subjects with LBCL who had prior ASCT, more than half of those subjects (18 of 31 subjects) relapsed within 12 months of ASCT treatment. The primary reason that subjects with DLBCL (N=139) were considered ineligible for ASCT included insufficient response to prior treatment (60 [43.2%] subjects), age 38 [27.3%] subjects), prior transplant (28 [20.1%] subjects), comorbidities (11 [7.9%] subjects), and ECOG performance status (2 [1.4%] subjects). Prior CAR T therapy was seen in 53 (38.1%) of the DLBCL patients and in 61 (38.9%) of the LBCL patients.

Over half of the subjects (96 [61.1%] subjects) with LBCL had primary refractory disease and three-quarters (119 [75.8%] subjects) were refractory to ≥2 consecutive prior lines of anti-lymphoma therapy. Prior systemic therapy given to iNHL subjects prior to transformation was included in the calculation of number of prior LOT.

Table 17: Prior Anticancer Therapies – aNHL Cohort, Expansion Part (Full Analysis Set)

Number of treated subjects, n (%)	aNHL Cohort		
	DLBCL (N=139)	Other Subtypes[a] (N=18)	LBCL (N=157)
Prior radiotherapy	58 (41.7%)	6 (33.3%)	64 (40.8%)
Prior stem cell transplant	26 (18.7%)	5 (27.8%)	31 (19.7%)
ASCT	26 (18.7%)	5 (27.8%)	31 (19.7%)
Subject relapsed ≤12 months after ASCT	15 (10.8%)	3 (16.7%)	18 (11.5%)
Allogeneic SCT	1 (0.7%)*	0	1 (0.6%)
Prior systemic therapy received			
Anti-CD20	139 (100%)	18 (100%)	157 (100%)
Anti-CD19	7 (5.0%)	0	7 (4.5%)
Alkylating-containing Agents	139 (100%)	18 (100%)	157 (100%)
Anthracyclines	137 (98.6%)	17 (94.4%)	154 (98.1%)
Nucleotide	115 (82.7%)	17 (94.4%)	132 (84.1%)
Topo inhibitor	93 (66.9%)	17 (94.4%)	110 (70.1%)
PI3K inhibitor	6 (4.3%)	0	6 (3.8%)
BCL2 inhibitor	3 (2.2%)	0	3 (1.9%)
PolyV	13 (9.4%)	4 (22.2%)	17 (10.8%)
CAR T	53 (38.1%)	8 (44.4%)	61 (38.9%)
Other	139 (100%)	18 (100%)	157 (100%)
Median number (min, max) of prior lines of anti-lymphoma therapy	3.0 (2, 11)	4.0 (2, 5)	3.0 (2, 11)
1	0	0	0
2	41 (29.5%)	5 (27.8%)	46 (29.3%)
3	47 (33.8%)	3 (16.7%)	50 (31.8%)
≥4	51 (36.7%)	10 (55.6%)	61 (38.9%)
Median time (min, max) from end of last-line anti-lymphoma therapy to first dose of epcoritamab (months) [e]	2.5 (0, 153)	2.4 (1, 17)	2.4 (0, 153)
Subjects with primary refractory disease[b]	82 (59.0%)	14 (77.8%)	96 (61.1%)
Subjects refractory to ≥2 consecutive lines of prior anti-lymphoma therapy[c]	104 (74.8%)	15 (83.3%)	119 (75.8%)
Last-line systemic antineoplastic therapy			
Refractory[c]	114 (82.0%)	16 (88.9%)	130 (82.8%)
No response	63 (45.3%)	11 (61.1%)	74 (47.1%)
Relapsed within 6 months after therapy completion	51 (36.7%)	5 (27.8%)	56 (35.7%)
Relapsed[d]	25 (18.0%)	2 (11.1%)	27 (17.2%)

Abbreviations: aNHL = aggressive B-cell non-Hodgkin lymphoma; ASCT = autologous stem cell transplantation; CAR T = chimeric antigen receptor T-cells; DLBCL= diffuse large B-cell lymphoma; LBCL = large B-cell lymphoma; max = maximum; min = minimum; SCT = stem cell transplantation.

[a] Other includes 9 subjects with high-grade B-cell lymphoma (HGBCL), 5 subjects with follicular lymphoma (FL) grade 3B and 4 subjects with primary mediastinal B-cell lymphoma (PMBCL).

[b] Subject was considered primary refractory if the subject is refractory to frontline anti-lymphoma therapy.

[c] Subject was considered refractory if the subject experienced disease progression or stable disease as best response or disease progression within 6 months after therapy completion.

[d] Subject was considered relapsed if the subject experienced disease progression >6 months after last treatment.

* One patient received both ASCT and allogenic SCT.

Data cutoff date: 31 Jan 2022

Source: Table 14.1.1.6.1

Concomitant medication

All 157 subjects received corticosteroids pre- and post-epcoritamab administration per the criteria specified in the protocol. Most commonly used medication types were antibacterials (87.3%),

analgesics (84.1%), antivirals (82.8%), Drugs for acid related disorders (66.2%). In total 71 (45.2%) subjects received concomitant allopurinol and 15 (9.6%) subjects received concomitant rasburicase; these medications were mostly used as prophylactic measures in subjects with high risk factors for tumor lysis syndrome. On-treatment transfusions were administered to 30 (19.1%) subjects, most commonly, packed red blood cells (27 [17.2%] subjects) or platelets (11 [7.0%] subjects).

Subsequent cancer therapies

In Table 31 the most subsequent anti-lymphoma therapies are summarized.

Table 18: Subsequent Anti-lymphoma Therapies – aNHL Cohort, Expansion Part (Full Analysis Set)

Number of Treated Subjects, n (%)	aNHL Cohort		
	DLBCL (N=139)	Other Subtypes[a] (N=18)	LBCL (N=157)
Subjects with any subsequent anti-lymphoma therapy	**48 (34.5%)**	**7 (38.9%)**	**55 (35.0%)**
Subsequent radiotherapy	**14 (10.1%)**	**1 (5.6%)**	**15 (9.6%)**
Subsequent CAR T therapy	**7 (5.0%)**	**1 (5.6%)**	**8 (5.1%)**
Subsequent stem cell transplant	**6 (4.3%)**	**2 (11.1%)**	**8 (5.1%)**
Autologous	1 (0.7%)	0	1 (0.6%)
Allogeneic	5 (3.6%)	2 (11.1%)	7 (4.5%)
Subjects received subsequent systemic drug therapy	**37 (26.6%)**	**4 (22.2%)**	**41 (26.1%)**
Generic name[b]			
Rituximab	21 (15.1%)	1 (5.6%)	22 (14.0%)
Lenalidomide	10 (7.2%)	0	10 (6.4%)
Investigational antineoplastic drugs	7 (5.0%)	2 (11.1%)	9 (5.7%)
Polatuzumab vedotin	8 (5.8%)	0	8 (5.1%)

Abbreviations: aNHL = aggressive B-cell non-Hodgkin lymphoma; ATC = Anatomical Therapeutic Chemical; CAR□T = chimeric antigen receptor T-cell; DLBCL= diffuse large B-cell lymphoma; LBCL = large B-cell lymphoma.
Note: Subjects are counted at most one time within each generic name, and at most one time per each ATC level.
[a] Other includes 9 subjects with high grade B-cell lymphoma (HGBCL), 5 subjects with follicular lymphoma (FL) grade 3B and 4 subjects with primary mediastinal B-cell lymphoma (PMBCL).
[b] Where incidence for LBCL was >5.0%.
Data cutoff date: 31□Jan□2022

- **Numbers analysed**

All efficacy analyses were performed on the FAS. The FAS population included 157 LBCL patients: 139 patients with DLBCL and 18 with other subtypes.

Sensitivity analyses were also performed for the PP set (N=150; subjects in the FAS with measurable disease at baseline and no important protocol deviations), RES (N=153; subjects who had measurable disease at baseline, and either at least 1 postbaseline disease evaluation or died within 60 days of first dose without postbaseline disease assessment), and the mRES (N=144; all subjects in the RES who had received at least 1 full dose of epcoritamab). The post-hoc retrospective central FISH analysis was performed in the FISH analysis set (n=88).

- **Outcomes and estimation**

As of the data cutoff date of 31 Jan 2022, median duration of follow-up was 10.7 months (range: 0.3, 17.9) and 11.0 months (range: 0.3, 17.9) for subjects with LBCL and DLBCL, respectively. In subjects with LBCL or DLBCL, the median number of cycles initiated was 5.0 (range: 1, 20) and the median duration of treatment was 4.1 months (range: 0, 18).

Primary endpoint

Table 32 presents the best ORR based on IRC assessment determined by Lugano criteria with PET scans for subjects in the aNHL expansion cohort.

Table 19: Best Overall Response Based on IRC Assessment, Lugano Criteria - aNHL Cohort, Expansion Part (Full Analysis Set)

	aNHL Cohort		
	DLBCL (N=139)	Other Subtypes[a] (N=18)	LBCL (N=157)
Overall response rate (ORR)[b]	86 (61.9%)	13 (72.2%)	99 (63.1%)
(95% CI)[c]	(53.3, 70.0)	(46.5, 90.3)	(55.0, 70.6)
Complete response rate (CR rate)	54 (38.8%)	7 (38.9%)	61 (38.9%)
(95% CI)[c]	(30.7, 47.5)	(17.3, 64.3)	(31.2, 46.9)
Best overall response			
Complete response (CR)	54 (38.8%)	7 (38.9%)	61 (38.9%)
Partial response (PR)	32 (23.0%)	6 (33.3%)	38 (24.2%)
Stable disease (SD)	4 (2.9%)	1 (5.6%)	5 (3.2%)
Progressive disease (PD)	33 (23.7%)	4 (22.2%)	37 (23.6%)
Not evaluable (NE)	16 (11.5%)	0	16 (10.2%)

Abbreviations: aNHL = aggressive B-cell non-Hodgkin lymphoma; CI = confidence interval; DLBCL = diffuse large B-cell lymphoma; IRC = independent review committee; LBCL = large B-cell lymphoma
[a] Other includes 9 subjects with high-grade B-cell lymphoma (HGBCL), 5 subjects with follicular lymphoma (FL) grade 3B, and 4 subjects with primary mediastinal B-cell lymphoma (PMBCL).
[b] CR+PR. Includes 10 subjects who had a PR or CR after an assessment of PD or indeterminate response (ie, pseudoprogression).
[c] Based on the Clopper and Pearson method.
Data cutoff date: 31 Jan 2022

Sensitivity analyses primary endpoint

The sensitivity analyses for were consistent with the primary analyses. Except the CT based ORR on IRC Assessment (Lugano Criteria) were a lower number of CRs was seen (21.6%; 95%CI: 15.3%, 28.9%) in LBCL patients (FAS).

Sensitivity analysis in PPS, RES and mRES were largely consistent with the results in the main primary endpoint efficacy analysis, with an ORR of 62.1% (95% CI: 53.3, 70.4) and CRR of 38.6% (95%CI: 30.3, 47.5) in the DLBCL PPS population (n=132), an ORR of 63.0% (95%CI: 54.2, 71.1) and CRR of 40.0% (95%CI: 31.7, 48.8) in the DLBCL RES population (n=135), an ORR of 66.9% (95%CI: 58.0, 75.0) and CRR of 42.5% (95%CI: 33.8, 51.6%) in the DLBCL mRES population (n=127).

While not explicitly stated in the endpoint definitions (statistical methods), the ORR, CRR, DOR and DOCR reported in the study results include patients that achieve PR/CR following previous PD (by Lugano) or IR (by LYRIC).

During the review, updated efficacy data were provided from the clinical DCO of 30 June 2022. At this DCO, the primary efficacy endpoint of ORR as assessed by the IRC using Lugano criteria was unchanged in DLBCL and LBCL patients. The CR rate as assessed by the IRC was also unchanged.

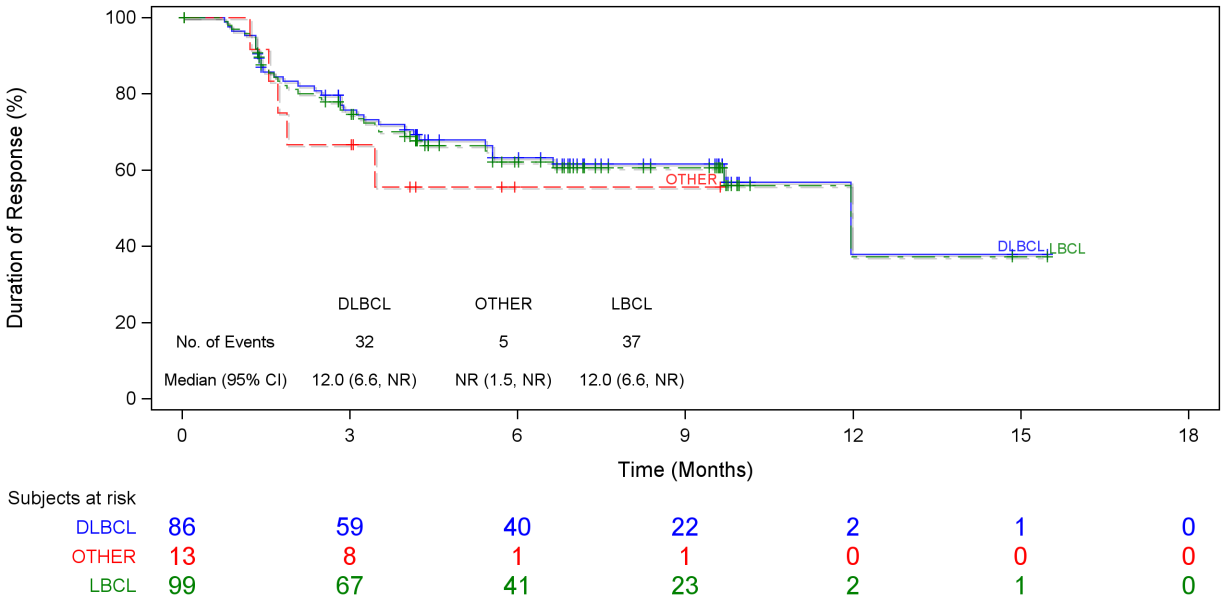
Secondary endpoints

Duration of response

In subjects with LBCL who had achieved PR or CR (n=99), the median DOR was 12.0 months (95% CI: 6.6, NR). The estimated percentage of subjects remaining in response at 3, 6, and 9 months was 74.6%, 62.2%, and 60.6%, respectively (Figure 16).

In subjects with DLBCL who had achieved PR or CR (n=86), the median DOR was 12.0 months (95% CI: 6.6, NR). The estimated percentage of subjects remaining in response at 3, 6, and 9 months was 75.8%, 63.3%, and 61.6%, respectively. In the other LBCL entities the median DoR was NR (1.5, NR).

Figure 10: Kaplan-Meier Plot of Duration of Response Based on IRC Assessment, Lugano Criteria - aNHL Cohort, Expansion Part (Full Analysis Set)



Abbreviations: aNHL = aggressive B-cell non-Hodgkin lymphoma; CI = confidence interval; DLBCL = diffuse large B-cell lymphoma; IRC = independent review committee; LBCL = large B-cell lymphoma; NR = not reached.
Data cutoff date: 31 Jan 2022
Source: Figure 14.2.1.9.1

As of the 30 June 2022 DCO, the updated median DOR (as assessed by the IRC using Lugano criteria) was 15.6 months (95% CI: 9.7, not reached [NR]) in all responders with DLBCL (with a median DOR follow-up time of 9.9 months) and 15.5 (9.7, NR) in LBCL patients. The applicant indicated that the median DOR is mature and remains unchanged after 5 more months of follow-up (median study duration follow-up of 20.0 months, based on DCO:18 November 2022; median DOR is 15.5 months (95% CI: 9.7, 20.8 months).

The reasons for censoring for the DOR analysis are presented by the current 31 January 2022 DCO and updated 30 June 2022 DCO in Table 33.

Table 20: DOR and Reasons for Censoring for January 2022 and June 2022 DCO

	31 January 2022 DCO	30 June 2022 DCO
	DLBCL (N=139)	DLBCL (N=139)
Number of Responders	86	86
Number of Events	32 (37.2%)	35 (40.7%)
Number of Censored	54 (62.8%)	51 (59.3%)
Reason for censoring		
Clinical Cutoff	45 (83.3%)	42 (82.4%)

New anti-lymphoma therapy	9 (16.7%)	9 (17.6%)
Withdrawal by subject	0	0
DOR (months)		
Median (95% CI)[a]	12.0 (6.6, NR)	15.6 (9.7, NR)
Estimate percentage of patients remaining in response (95% CI)[a]		
3-month	75.8% (65.0%, 83.7%)	75.8% (65.0%, 83.7%)
6-month	63.3% (51.5%, 73.0%)	66.5% (55.0%, 75.7%)
9-month	61.6% (49.7%, 71.5%)	63.6% (51.9%, 73.2%)
12-month	37.9% (10.1%, 66.4%)	57.2% (44.4%, 68.1%)
15-month	37.9% (10.1%, 66.4%)	57.2% (44.4%, 68.1%)

DLBCL = diffuse large B-cell lymphoma; DCO = data cut-off; DOR = duration of response; NR = not reached.

a. Based on Kaplan-Meier estimate

Note 1: Primary definition of DOR will account for subsequent anti-lymphoma therapy and censor DOR at the last evaluable tumour assessment on or prior to the date of subsequent anti-lymphoma therapy. Symbol '+' indicated a censored value.

Source: Table q116_1; Table 14.2.1.7.1 (DCO: 30 June 2022).

The secondary censoring definition of DOR differed from the first definition that patients who received anti-cancer medication are continued to be followed up until progression or death (or censored at the DCO date).

Table 21: **DOR by Primary and Secondary Censoring Rules for January 2022 and June 2022 DCO**

	31 January 2022 DCO		**30 June 2022 DCO**	
	Primary definition DLBCL (N=139)	**Secondary definition DLBCL (N=139)**	**Primary definition DLBCL (N=139)**	**Secondary definition DLBCL (N=139)**
Number of Responders	86	86	86	86
Number of Events	32 (37.2%)	34 (39.5%)	35 (40.7%)	37 (43.0%)
Number of Censored	54 (62.8%)	52 (60.5%)	51 (59.3%)	49 (57.0%)
Reason for censoring				
Clinical Cutoff	45 (83.3%)	52 (100%)	42 (82.4%)	49 (100%)

	31 January 2022 DCO		30 June 2022 DCO	
	Primary definition DLBCL (N=139)	**Secondary definition DLBCL (N=139)**	**Primary definition DLBCL (N=139)**	**Secondary definition DLBCL (N=139)**
New anti-lymphoma therapy	9 (16.7%)	NA	9 (17.6%)	NA
Withdrawal by subject	0	0	0	0
DOR (months)				
Median (95% CI)[a]	12.0 (6.6, NR)	11.1 (6.8, NR)	15.6 (9.7, NR)	15.5 (9.7, NR)

DLBCL = diffuse large B-cell lymphoma; DCO = data cut-off; DOR = duration of response; NR = not reached.

Note 1: Primary definition of DOR will account for subsequent anti-lymphoma therapy and censor DOR at the last evaluable tumour assessment on or prior to the date of subsequent anti-lymphoma therapy. Secondary definition of DOR is irrespective of subsequent therapy and will not account for subsequent anti-lymphoma therapy. Symbol '+' indicated a censored value.

a. Based on Kaplan-Meier estimate.

Source: Tables q116_1, q117_1, q117_2; Table 14.2.1.7.1 (30JUN 2022 DCO)

In a sensitivity analysis which regarded start of new therapy as an event the updated median DOR in DLBCL patients was 12.0 months (95% CI: 5.6, NR).

Duration of complete response

In subjects with LBCL, the median DOCR was 12.0 months (95% CI: 9.7, NR). The estimated percentage of subjects remaining in response at 3, 6, and 9 months was 96.0%, 86.3%, and 86.3%, respectively.

In the DLBCL cohort, the median DOCR was 12.0 months (95% CI: 9.7, NR). The estimated percentage of subjects remaining in response at 3, 6, and 9 months was 95.7%, 85.3%, and 85.3%, respectively.

As of the 30 June 2022 DCO, the updated median DOCR (as assessed by the IRC using Lugano criteria) was not yet reached (95% CI: 14.3, NR) in DLBCL patients (with a median DOCR follow-up time of 9.7 months). The median duration was the same in LBCL patients. Using the secondary definition (see DOR) the median DOCR was NR (95%CI: 12.0, NR) in DLBCL patients. In a sensitivity analysis which regarded start of new therapy as an event the updated median DOCR was NR (95%CI: 10.4, NR) in DLBCL patients.

PFS

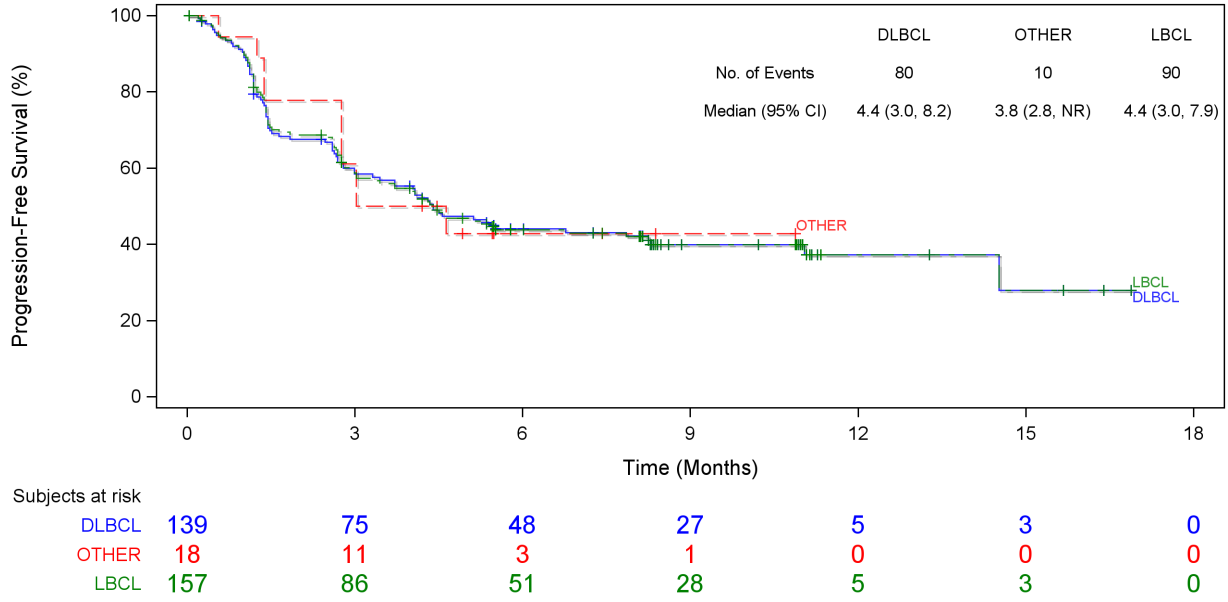
Table 35 presents the PFS based on IRC assessment (Lugano criteria) per the primary definition for subjects in the aNHL expansion cohort. A Kaplan-Meier plot of PFS (primary definition) based on IRC assessment is presented in Table 35 and Figure 17 for subjects in the aNHL expansion cohort. PFS according to the secondary definition is in line with the primary definition. The median PFS in subjects with DLBCL was essentially unchanged at the Jun-30-2022 DCO, with a median PFS of 4.4 months (95% CI: 3.0, 8.8) at the 30-Jun-2022 DCO.

Table 22: Progression-free Survival (Primary Definition) Based on IRC Assessment Lugano Criteria - aNHL Cohort, Expansion Part (Full Analysis Set)

	aNHL Cohort		
	DLBCL (N=139)	Other Subtypes[a] (N=18)	LBCL (N=157)
Number of events	80 (57.6%)	10 (55.6%)	90 (57.3%)
Number of censored	59 (42.4%)	8 (44.4%)	67 (42.7%)
PFS (months)			
Min, Max	0.0+, 16.9+	0.6, 10.9+	0.0+, 16.9+
25% quartile (95% CI)[b]	1.4 (1.2, 1.8)	2.8 (0.6, 3.0)	1.4 (1.2, 2.5)
Median (95% CI)[b]	4.4 (3.0, 8.2)	3.8 (2.8, NR)	4.4 (3.0, 7.9)
75% quartile (95% CI)[b]	NR (14.5, NR)	NR (4.6, NR)	NR (14.5, NR)
Estimated percentage of subjects remaining progression free (95% CI)[b]			
6-month	44.1% (35.4, 52.4)	42.9% (19.7, 64.3)	43.9% (35.7, 51.7)
9-month	39.9% (31.2, 48.4)	42.9% (19.7, 64.3)	39.9% (31.7, 48.0)
12-month	37.2% (27.8, 46.6)	NR (NR, NR)	37.2% (28.1, 46.3)

Abbreviations: aNHL = aggressive B-cell non-Hodgkin lymphoma; CI = confidence interval; DLBCL = diffuse large B-cell lymphoma; IRC = independent review committee; LBCL = large B-cell lymphoma; Max = maximum; Min = minimum; NR = not reached; PFS = progression-free survival.
Note: Symbol '+' indicates a censored value.
[a] Other includes 9 subjects with high-grade B-cell lymphoma (HGBCL), 5 subjects with follicular lymphoma (FL) grade 3B and 4 subjects with primary mediastinal B-cell lymphoma (PMBCL).
[b] Based on Kaplan-Meier estimate.
Data cutoff date: 31 Jan 2022
Source: Table 14.2.1.12.1

Figure 11: Kaplan-Meier Plot of Progression-free Survival (Primary Definition) Based on IRC Assessment, Lugano Criteria - aNHL Cohort, Expansion Part (Full Analysis Set)



TTR

For subjects with LBCL (based on 99 responders) and for subjects with DLBCL (based on 86 responders), median TTR based on IRC assessment was 1.4 months (range: 1.0, 8.4). For both subjects with LBCL (based on 61 responders) and subjects with DLBCL (based on 54 responders), median TTCR based on IRC assessment was 2.7 months (range: 1.2, 11.1).

LYRIC

Using LYRIC the ORR was 63.1% (N=99 [95%CI 53.3%, 70.0%]) with a CR in 38.9% (N=61 [95%CI 30.7%, 47.5%] in LBCL patients. The TTR and TTCR were identical for Lugano criteria and LYRIC. Both the median DOR and median DOCR were NR (9.7, NR) months and the median PFS was 8.3 (4.4, NR) months in LBCL patients.

OS

Table 36 presents the OS for subjects in the aNHL expansion cohort. A Kaplan-Meier plot of OS for the aNHL expansion cohort is presented in Table 36 and Figure 18. The median OS at the 30-Jun-2022 DCO was 18.5 months (range: 11.7, NR).

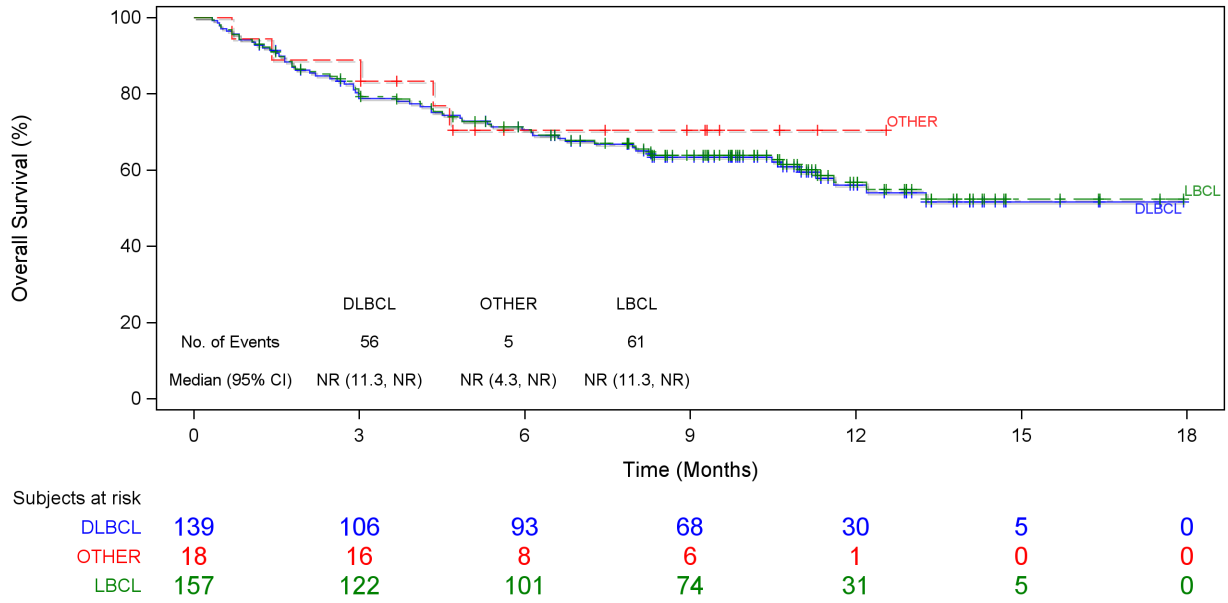
Table 23: Overall Survival – aNHL Cohort, Expansion Part (Full Analysis Set)

	aNHL Cohort		
	DLBCL (N=139)	Other Subtypes[a] (N=18)	LBCL (N=157)
Number of events	56 (40.3%)	5 (27.8%)	61 (38.9%)
Number of censored	83 (59.7%)	13 (72.2%)	96 (61.1%)
OS (months)			
Min, max	0.3, 17.9+	0.7, 12.6+	0.3, 17.9+
25% quartile (95% CI)[b]	4.5 (2.9, 6.7)	4.6 (0.7, NR)	4.5 (2.9, 6.7)
Median (95% CI)[b]	NR (11.3, NR)	NR (4.3, NR)	NR (11.3, NR)
75% quartile (95% CI)[b]	NR (NR, NR)	NR (NR, NR)	NR (NR, NR)
Estimate percentage of subjects remaining alive (95% CI)[b]			

	aNHL Cohort		
	DLBCL (N=139)	Other Subtypes[a] (N=18)	LBCL (N=157)
6-month	70.6% (62.2, 77.5)	70.5% (42.8, 86.6)	70.6% (62.7, 77.2)
9-month	63.4% (54.6, 71.0)	70.5% (42.8, 86.6)	63.9% (55.6, 71.1)
12-month	56.1% (46.1, 64.9)	70.5% (42.8, 86.6)	56.9% (47.3, 65.4)
15-month	51.6% (40.6, 61.6)	NR (NR, NR)	52.4% (41.7, 62.1)
18-month	NR (NR, NR)	NR (NR, NR)	NR (NR, NR)

Abbreviations: aNHL = aggressive B-cell non-Hodgkin lymphoma; CI = confidence interval; DLBCL = diffuse large B-cell lymphoma; LBCL = large B-cell lymphoma; Max = maximum; Min = minimum; NR = not reached; OS = overall survival.
Note: Symbol '+' indicates a censored value.
[a] Other includes 9 subjects with high-grade B-cell lymphoma (HGBCL), 5 subjects with follicular lymphoma (FL) grade 3B and 4 subjects with primary mediastinal B-cell lymphoma (PMBCL).
[b] Based on Kaplan-Meier estimate.
Data cutoff date: 31 Jan 2022
Source: Table 14.2.1.17

Figure 12: Kaplan-Meier Plot of Overall Survival - aNHL Cohort, Expansion Part (Full Analysis Set)



Abbreviations: aNHL = aggressive B-cell non-Hodgkin lymphoma; CI = confidence interval; DLBCL = diffuse large B-cell lymphoma; LBCL = large B-cell lymphoma; NR = not reached.
Data cutoff date: 31 Jan 2022
Source: Figure 14.2.1.13.1

TTNT

The median TTNT was 7.4 months (95% CI: 5.9, 10.8) with 82 (52.2%) LBLC subjects experiencing a TTNT event. Median TTNT was 8.2 months (95% CI: 6.0, 13.9) among subjects with DLBCL.

MRD

The overall number of subjects with MRD results per PBMC assay (using clonoSEQ next-generation sequencing assay) was low (n=55). The incidence of overall MRD negativity per PBMC assay using the 10^{-5} cutoff is N= 37 (67.3%; 95% CI 53.3%, 79.3%) in LBCL patients and N=32 (68.1%; 95% CI 52.9%, 80.9%) in 47 evaluable DLBCL patients. There are no very large differences in frequencies of MRD negativity when the 10^{-4} or 10^{-6} threshold are used. A low correlation of MRD with clinical response was observed, as evidenced by a high rate of subjects with PD who were assessed as MRD-negative.

For the ctDNA assay, the overall MRD negativity rate (at any time point) among subjects with LBCL who were MRD-evaluable (N=107) was 45.8% (95% CI: 36.1, 55.7) using the clonoSEQ next-generation sequencing assay. Median duration of MRD negativity was not reached, and an estimated 78.7% of subjects (95% CI: 62.4, 88.5) were remaining in MRD negativity at 6 months. Subjects who achieved MRD-negative status had improved PFS compared with subjects who were MRD-positive, see Figure ***19*** DOR per MRD and response status is shown in Figure ***20***.

Figure 13: Kaplan-Meier Plot of PFS Based on IRC Assessment, Lugano Criteria, Primary Definition by MRD Negativity Status per ctDNA Assay - Subjects with LBCL, aNHL Cohort, Expansion Part (MRD Evaluable Set)

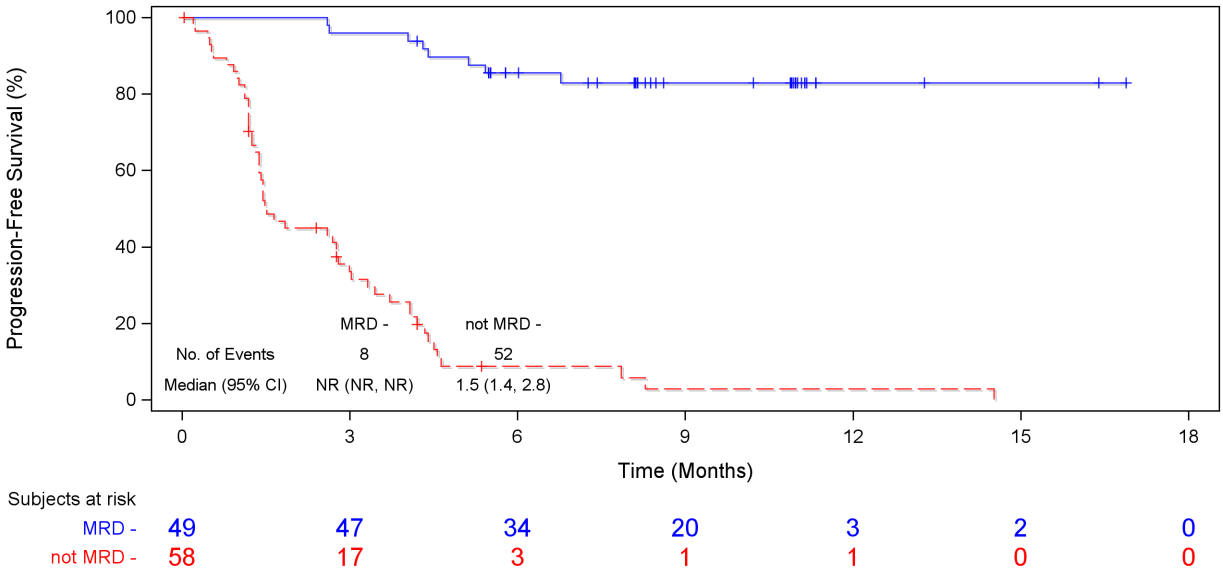
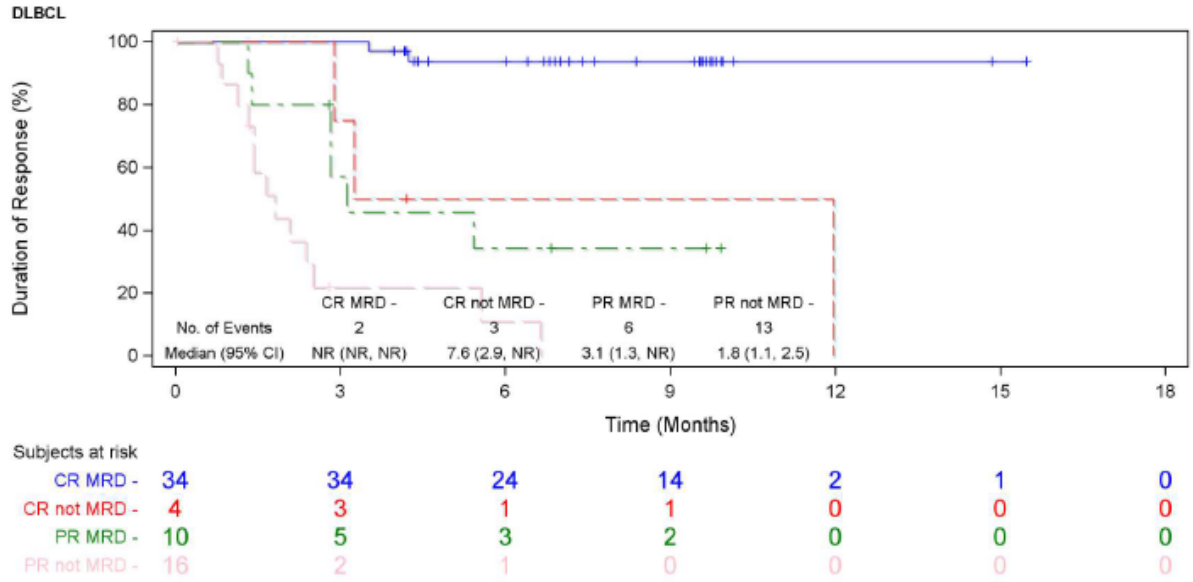


Figure 14: Kaplan-Meier Plot of Duration of Response based on IRC Assessment, Lugano Criteria by Best Overall Response and MRD Negativity per ctDNA Assay



FACT-Lym Patient-Reported Outcomes

Compliance was >80% at most time points, being lower than this at C3D1 (35.8%), C13D1 (74.1%), C14D1 (68.2%), C15D1 (75.0%), and EOT (54.3%) for subjects with LBCL. The mean scores for six

selected Fact-Lym questions considered related to key symptoms of lymphoma are provided in Table 37.

Table 24*:* Mean Scores for 6 Fact-Lym Symptoms While on Treatment - aNHL Cohort, Expansion Part (Full Analysis Set)

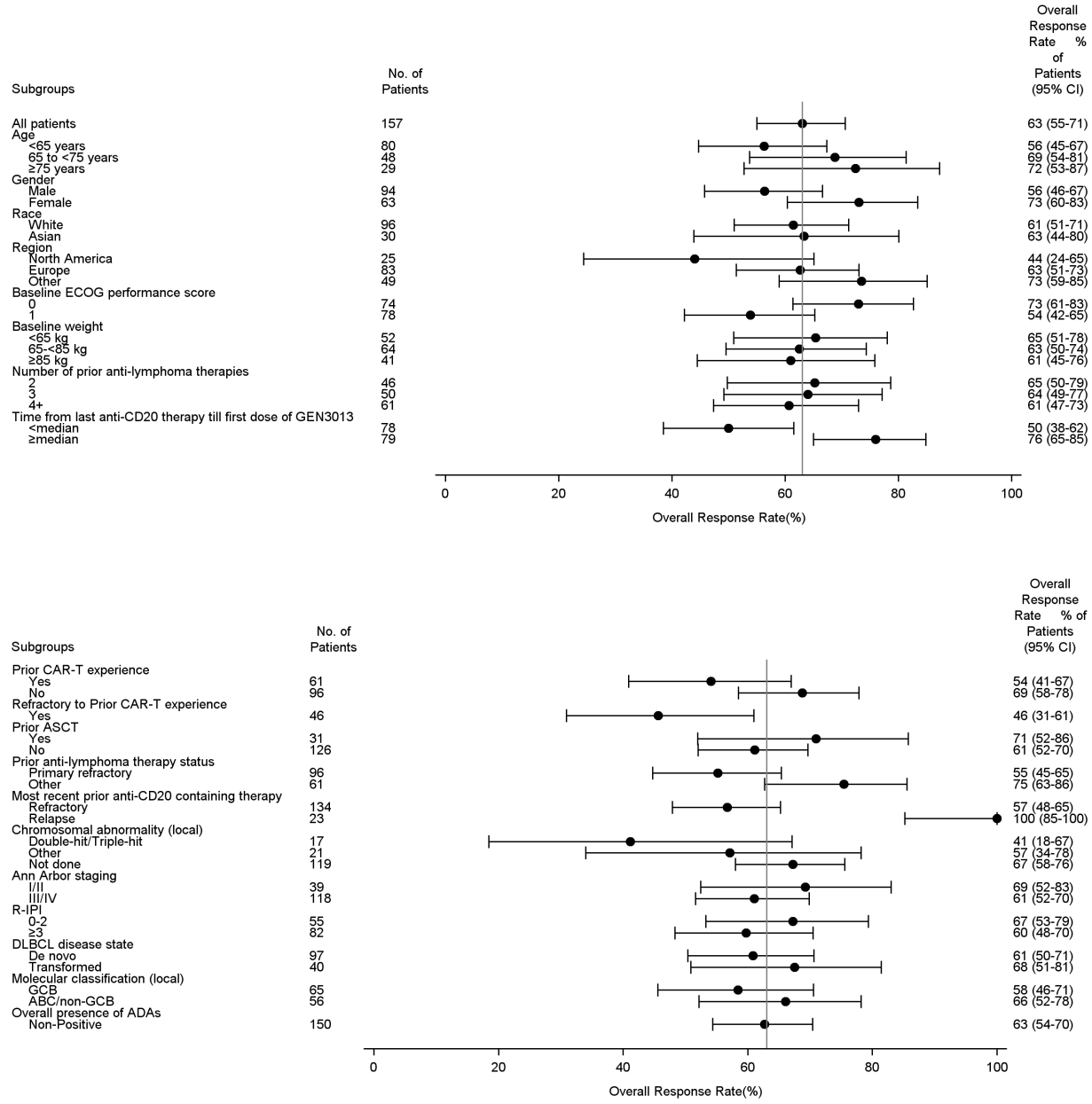
	Mean (Standard Deviation) Score on Treatment			
	DLBCL (N=139)		LBCL (N=157)	
FACT-Lym Symptom	C2D1 (n=108)	C13D1 (n=19)	C2D1 (n=123)	C13D1 (n=20)
P2 (body pain)	1.3 (1.25)	0.4 (0.60)	1.3 (1.25)	0.4 (0.59)
BRM3 (fever)	0.4 (0.85)	0.0 (0.00)	0.4 (0.83)	0.0 (0.00)
ES3 (night sweats)	0.5 (0.80)	0.2 (0.42)	0.5 (0.86)	0.2 (0.41)
GP1 (lack of energy)	1.8 (1.12)	0.6 (0.61)	1.8 (1.13)	0.6 (0.60)
BMT6 (tires easily)	1.8 (1.11)	0.9 (0.66)	1.8 (1.10)	0.9 (0.64)
C2 (weight loss)	0.8 (0.93)	0.1 (0.32)	0.7 (0.92)	0.1 (0.31)

Abbreviations: C2D1 = Cycle 2 Day 1; C13D1 = Cycle 13 Day 1; DLBCL = diffuse large B-cell lymphoma; LBCL = large B-cell lymphoma.
Data cutoff date: 31 Jan 2022

- **Ancillary analyses**

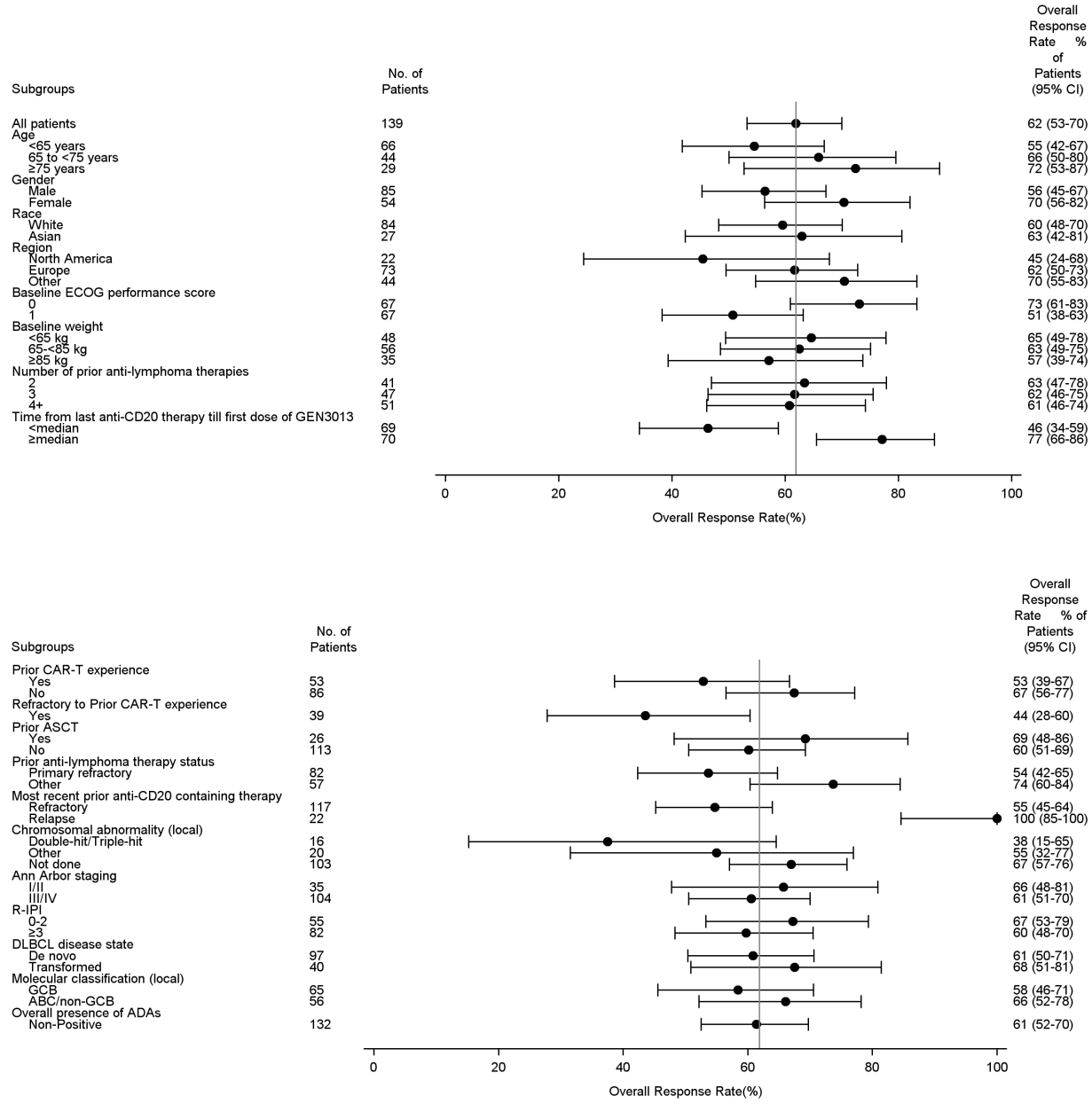
A forest plot of ORR in prespecified subgroups by IRC assessment using the Lugano criteria is presented in Figure 21 for subjects with LBCL and in Figure 22 for subjects with DLBCL.

Figure 15: Forest Plot of Overall Response Rate in Prespecified Subgroups Based on IRC Assessment Determined by Lugano Criteria - LBCL Subjects in aNHL Cohort, Expansion Part (Full Analysis Set)



Abbreviations: ADA = anti-drug antibody; aNHL = aggressive B-cell non-Hodgkin lymphoma; ASCT = autologous stem cell transplantation; CAR T = Chimeric antigen receptor T-cell; CI = confidence interval; DLBCL= diffuse large B-cell lymphoma; ECOG = Eastern Cooperative Oncology Group; GCB = germinal center B-cell; IHC = immunohistochemistry; IPI = International Prognostic Index; LBCL= large B-cell lymphoma.
Note: Results of response in subgroups by local laboratory analysis of chromosomal abnormality are not discussed due to availability of data from a more robust retrospective central analysis by FISH.
Data cutoff date: 31 Jan 2022
Source: Figure 14.2.1.1.2

Figure 16: Forest Plot of Overall Response Rate in Prespecified Subgroups Based on IRC Assessment Determined by Lugano Criteria - DLBCL Subjects in aNHL Cohort, Expansion Part (Full Analysis Set)



Abbreviations: ADA = anti-drug antibody; aNHL = aggressive B-cell non-Hodgkin lymphoma; ASCT = autologous stem cell transplantation; CAR T = Chimeric antigen receptor T-cell; CI = confidence interval; DLBCL= diffuse large B-cell lymphoma; ECOG = Eastern Cooperative Oncology Group; GCB = germinal center B-cell; IHC = immunohistochemistry; IPI = International Prognostic Index.
Note: Results of response in subgroups by local laboratory analysis of chromosomal abnormality are not discussed due to availability of data from a more robust retrospective central analysis by FISH.
Data cutoff date: 31 Jan 2022
Source: Figure 14.2.1.1.1

ORR in Other LBCL entities

Among the 5 subjects with FL grade 3B, 3 subjects had a CR and 2 subjects had a PR. The DOR ranged between 1.22- 5.95 (ongoing).

Among the 9 subjects with HGBCL, 2 subjects had a CR, 2 subjects had a PR, 1 subject had SD, and 4 subjects had PD. The DOR ranged between 1.87-9.63 (ongoing).

Among the 4 subjects with PMBCL, 2 subjects had a CR and 2 subjects had a PR. DOR range 0.03 (ongoing) – 8.38 (ongoing).

Table 25: Composite Efficacy Information for Subjects with aNHL Subtypes Other Than DLBCL Based on IRC Assessment, Lugano Criteria - aNHL Cohort, Expansion Part (Full Analysis Set)

Subject Number	aNHL Subtype	BOR (Trial Day)	First Response (Trial Day)	Trial Day of PD	DoR (months)	PFS (months)	
						Primary PFS	Secondary PFS
	FL3B	CR (167)	CR (167)	NA	4.17+	5.49+	5.49+
	FL3B	PR (48)	PR (48)	84	1.22	2.76	2.76
	FL3B	CR (80)	CR (80)	NA	3.06+	4.21+	4.21+
	FL3B	CR (226)	CR (226)	NA	5.95+	7.43+	10.81+
	FL3B	PR (41)	PR (41)	NA	1.71	3.02	3.02
	HGBL	PD (17)	NA	17	NA	0.56	0.56
	HGBL	PR (36)	PR (36)	92	1.87	3.02	3.02
	HGBL	PD (42)	NA	42	NA	1.38	1.38
	HGBL	CR (79)	CR (79)	NA	9.63+	10.87+	10.87+
	HGBL	PD (38)	NA	38	NA	1.25	1.25
	HGBL	PR (37)	PR (37)	NA	3.45	4.63	4.63
	HGBL	CR (136)	CR (136)	NA	3.02+	4.47+	4.47+
	HGBL	SD (45)	NA	84	NA	2.76	2.76
	HGBL	PD (42)	NA	42	NA	1.38	1.38
	PMBCL	PR (38)	PR (38)	84	1.54	2.76	2.76
	PMBCL	CR (43)	CR (43)	NA	4.07+	5.45+	5.45+
	PMBCL	CR (82)	CR (82)	NA	5.72+	8.38+	8.38+
	PMBCL	PR (150)	PR (150)	NA	0.03+	4.93+	4.93+

Abbreviations: aNHL = aggressive B-cell non-Hodgkin lymphoma; BOR = best overall response; CR = complete response; DLBCL = diffuse large B-cell lymphoma; DoR = duration of response; FL = follicular lymphoma; HGBL = high grade B-cell lymphoma; NA = not applicable; NE = not evaluable; PD = progressive disease; PFS = progression-free survival; PMBCL = primary mediastinal B-cell lymphoma; PR = partial response; SD = stable disease.
Note: Symbol '+' indicates a censored value.
Note: BOR was also the first documented response at this data cutoff.
Data cutoff date: 31 Jan 2022

ORR in HGBL subjects with *MYC* and *BCL2* and/or *BCL6* rearrangements

Efficacy analysis based on FISH results were performed post-hoc. Based on central laboratory FISH analysis of screening tumor tissue available from 88 subjects enrolled in the DLBCL cohort, 12 (13.6%) subjects had tumors with MYC, BCL2, and/or BCL6 rearrangements. The ORR (CR + PR) in subjects with HGBCL by FISH (N=12) was 50.0% (95% CI: 21.1, 78.9), with 4 (33.3%) and 2 (16.7%) subjects achieving best response of CR and PR, respectively. For subjects with HGBCL by FISH (N=12), the median DOR among all responders was 12.0 months (95% CI: 1.1, NR), with 83.3% of subjects remaining in response at 6 and 9 months.

Four additional subjects enrolled as having DLBCL, who did not have central FISH results available, were classified as having DH/TH disease (HGBL with MYC and BCL2 and/or BCL2 rearrangements) based on local FISH analysis. Two of these 4 subjects achieved a best response of CR based on IRC assessment as determined by Lugano criteria. In addition, there were 2 subjects with DH per central or local FISH analysis among the 9 HGBCL subjects. In these 18 subjects with DLBCL/HGBCL DH/TH

lymphomas ORR was50.0% [95% CI: 26.0, 74.0] and CRR was33.3% [95% CI: 13.3, 59.0], which is comparable to results in the 139 subjects with DLBCL, where ORR was 61.9% (95% CI: 53.3, 70.0) and the CR rate was 38.8% (95% CI: 30.7, 47.5). The median DOR for all responders and in subjects with complete response were 12.0 months (95% CI: 1.1, NR) and 12.0 months (95% CI: 5.6, NR).

Response results in Stage 1 and Stage 2 of study

In the response to the 1st LoQ the applicant provided separate ORR and DoR results for patients who were recruited in Stage 1 and Stage 2.

Table 26: ORR and DOR Based on IRC Assessment, Lugano Criteria - GCT3013-01 Expansion Part – Subjects with DLBCL in aNHL Cohort (FAS) Subset of Subjects in Stage 1 and Stage

	DLBCL Stage 1 N=71	**DLBCL Stage 1 interim N = 26**	**DLBCL Stage 2 N = 68**
ORR[a]	43 (60.6%)	16 (61.5%)	43 (63.2%)
(95% CI)[b]	(48.3%, 72.0%)	(40.6%, 79.8%)	(50.7%, 74.6%)
CR	22 (31.0%)	7 (26.9%)	32 (47.1%)
PR	21 (29.6%)	9 (34.6%)	11 (16.2%)
DOR			
Number of Responders	43	16	43
Number of Events	23 (53.5%)	9 (56.3%)	9 (20.9%)
Number of Censored	20 (46.5%)	7 (43.8%)	34 (79.1%)
Reason for censoring			
Clinical Cutoff	17 (85.0%)	5 (71.4%)	28 (82.4%)
New anti-lymphoma therapy	3 (15.0%)	2 (28.6%)	6 (17.6%)
DOR (months)			
Median (95% CI)[c]	6.6 (2.8, NR)	5.4 (1.3, NR)	NR (NR, NR)

aNHL = aggressive non-Hodgkin lymphoma; CI = confidence interval; CR = complete response; DLBCL = diffuse large B-cell lymphoma; DOR = duration of response; NR = Not reached; ORR = Overall response rate; PR = partial response.

Note: Percentages calculated based on number of subjects in FAS. Primary definition of DOR will account for subsequent anti-lymphoma therapy and censor DOR at the last evaluable tumour assessment on or prior to the date of subsequent anti-lymphoma therapy. Symbol '+' indicated a censored value.

a. CR+PR

b. Based on the Clopper and Pearson method.

c. Based on Kaplan-Meier estimate.

ORR in patients with low vs normal/increased B cell counts at baseline

A summary of the ORR and CRR based on B-cell count at baseline is presented in **Error! Reference source not found.**.

Table 27: ORR and CRR Based on IRC Assessment, Lugano Criteria, by B-Cell Count at Baseline - GCT3013-01 Expansion Part – DLBC and LBCL Subjects - Full Analysis Set

	DLBCL (N = 139)		
	Low B-Cell Count at Baseline (< 100 Cells/uL) (n=126)	Normal/Increase B-Cell Count at Baseline (≥ 100 Cells/uL) (n=6)	Missing B-Cell Count at Baseline (≥ 100 Cells/uL) (n=7)
ORR			
No of Response (%) [a]	76 (60.3%)	5 (83.3%)	5 (71.4%)
(95% CI) [b]	(51.2%, 68.9%)	(35.9%, 99.6%)	(29.0%, 96.3%)
CRR			
No of Response (%)	47 (37.3%)	3 (50.0%)	4 (57.1%)
(95% CI) [b]	(28.9%, 46.4%)	(11.8%, 88.2%)	(18.4%, 90.1%)
	LBCL (N = 157)		
	Low B-Cell Count at Baseline (< 100 Cells/uL) (n=143)	Normal/Increase B-Cell Count at Baseline (≥ 100 Cells/uL) (n=6)	Missing B-Cell Count at Baseline (≥ 100 Cells/uL) (n=8)
ORR			
No of Response (%)[a]	88 (61.5%)	5 (83.3%)	6 (75.0%)
(95% CI) [b]	(53.0%, 69.5%)	(35.9%, 99.6%)	(34.9%, 96.8%)
CRR			
No of Response (%)	54 (37.8%)	3 (50.0%)	4 (50.0%)
(95% CI) [b]	(29.8%, 46.2%)	(11.8%, 88.2%)	(15.7%, 84.3%)

Note: Percentages are calculate based on n.

a. CR + PR

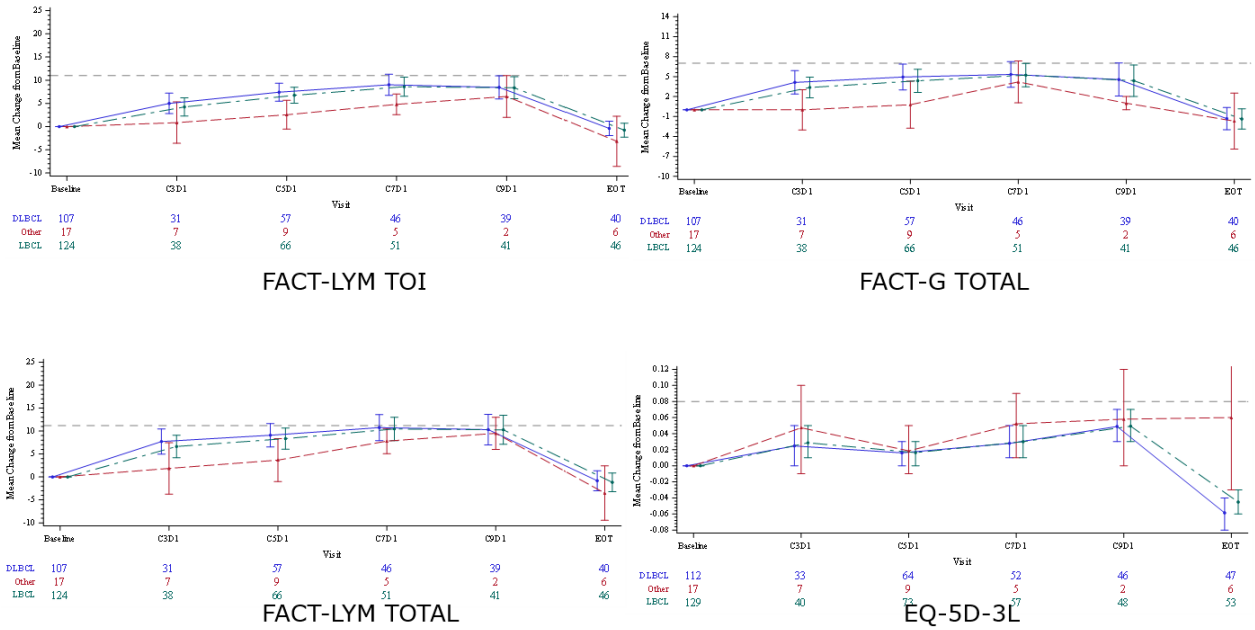
b. Based on the Clopper and Pearson method.

Note: Table 126_1a: Data Cutoff: 30JUN2022.

FACT-LYM TOI

For subjects with LBCL, steady and consistent improvements in TOI were observed, with mean (standard deviation) scores improving from 79.5 (19.93) at baseline (C1D1, N=140) to 94.0 (13.78) at C9D1 (N=45), the final on-treatment time point measured.

Figure 17: Mean Change from Baseline in FACT-Lym Trial Outcome Index, FACT-G, FACT LYM and EQ-5D-3L - aNHL Cohort, Expansion Part (PRO evaluable Set)

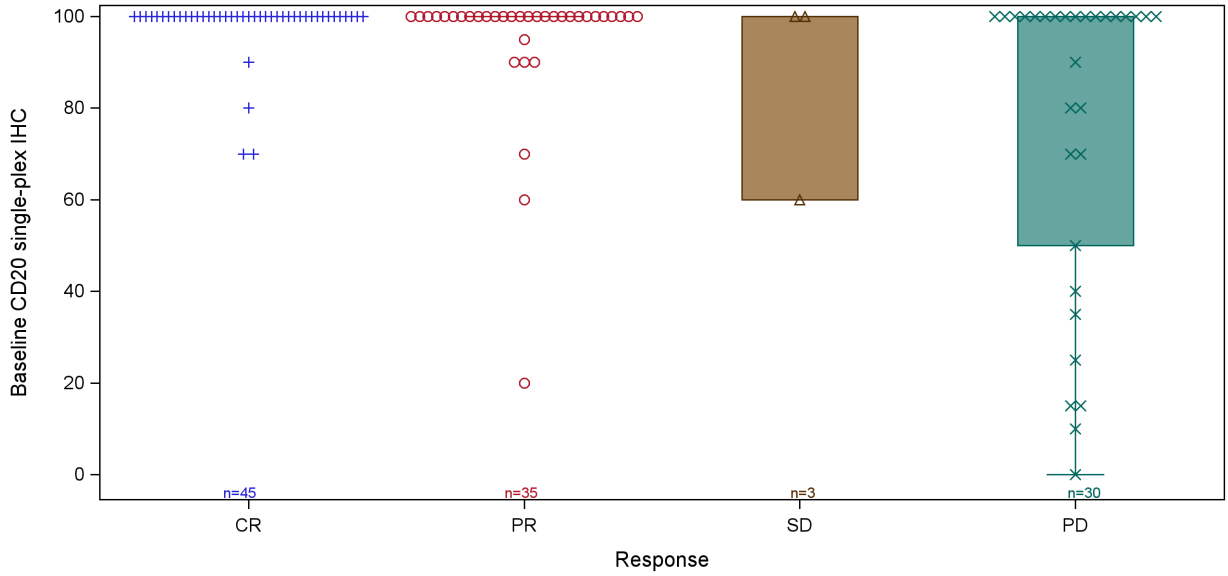


Abbreviations: aNHL = aggressive B-cell non-Hodgkin lymphoma; C = Cycle; D = Day; DLBCL = diffuse large B-cell lymphoma; LBCL = large B-cell lymphoma; PRO = patient-reported outcome.
Note: Horizontal reference line indicates minimum important difference (MID=11).
Data cutoff date: 31 Jan 2022
Source: Figure 14.2.3.5.1

CD20 expression

Per the local laboratory analyses 146 (93.0%) subjects with LBCL were positive for CD20 at baseline. Baseline CD20 expression based on CD20 single-plex IHC is plotted per response group in Figure 24. Per these central laboratory analyses, the median baseline CD20 was 100.0% (range 0% to 100%). Overall, high expression of CD20 was observed in almost all IHC-evaluable subjects, in spite of prior CD20 treatments, and patients with low CD20 expression represent a minor proportion of the heavily pre-treated patient population. Expression levels below 50% were observed in 8 out of 113 central immunohistochemistry (IHC) evaluable and response evaluable patients. Low levels of expression were observed in some of the non- responders (PD), but one low expression was also observed in a subject with PR.

Figure 18: Baseline CD20 Expression by Response Group - aNHL Cohort Subjects with LBCL, Expansion Part (Full Analysis Set)



Abbreviations: aNHL = aggressive B-cell non-Hodgkin lymphoma; CR = complete response; LBCL = large B-cell lymphoma; PD = progressive disease; PR = partial response; SD = stable disease.
Data cutoff date: 31 Jan 2022
Source: Figure 14.2.3.3.4

Regarding Figure 24: Baseline CD20 Expression by Response Group - aNHL Cohort Subjects with LBCL, Expansion Part (Full Analysis Set), of the 157 patients in the aNHL cohort, 124 had CD20 expression by central lab (Table 34) and 141 (sum of CR, PD, PR, and SD) had response assessed (Table 40). Forty-four patients were excluded from analysis, of which 33 had no tissue evaluable for CD20 assessment, and 11 patients had CD20 expression but had a BOR of NE (response not evaluable).

Table 28: Baseline CD20 by Central Lab - GCT3013-01 Expansion Part - Subjects in aNHL Cohort - Full Analysis Set

Baseline CD20 Single-Plex IHC (Central Lab) Assessment Category	BOR IRC Lugano Assessment					
	CR	PD	PR	SD	NE	Total
Missing	16 (48.5%)	7 (21.2%)	3 (9.1%)	2 (6.1%)	5 (15.2)	33
Not Missing	45 (36.3%)	30 (24.2%)	35 (28.2%)	3 (2.4%)	11 (8.9%)	124
Total	61	37	38	5	16	157

BOR = best overall response; CR = complete response; IHC = immunohistochemistry; PD = progressive disease; PR = partial response; NE = not evaluable; SD = stable disease

Note: Percentages are calculate based on n.

At the request of the CHMP the applicant provided efficacy data in patients with CD20 expression below 50% by central laboratory assessment (DCO 30 Jun 2023).

Table 29: **Composite Efficacy Information for Subjects with Baseline CD20 Single-Plex < 50% by Central Lab (GCT3013-01 Expansion Part - Subjects in aNHL Cohort - Full Analysis Set)**

			Lugano IRC				
Subject Age range/ sex/race/Dx[a]	**Central Lab Result**	**OS (month)**	**BOR/ (Study Day)**	**First Response/ (Study Day)**	**PD Study Day**	**DOR (month)**	**Primary PFS(month)**
70-80/F/W/D	20%	14.2+	PR/ 48	PR/ 48	168	3.98	5.52
60-70/M/W/D	15%	0.8	PD/ 7		7		0.23
40-50/F/W/D	25%	1.2	PD/ 14		14		0.46
50-60/M/W/D	35%	15.2	PD/ 43		43		1.41
30-40/F/W/H	10%	1.4	PD/ 38		38		1.25
20-30/M/W/D	0	2.2	PD/ 36		36		1.18
40-50/M/W/D	15%	6.7	PD/ 36		36		1.18
40-50/F/W/D	40%	6.6	PD/ 31		31		1.02

BOR = best overall response; D = (D)LBCL or diffuse large B-cell lymphoma; DOR = duration of response; F = female H = (H)GBCL or high-grade B-cell lymphoma; IRC = Independent Review Committee; M = male; OS = overall survival; PD = progressive disease; PFS = progression-free survival; W = White

a. Age range in years.; Note: + symbol indicates censored values.; Snapshot date: 30JUL2022; DCO: 30.06.2022.

Biomarkers

Median concentration values over time are provided for subjects with LBCL for the following cytokines: IFN-γ, IL-6, IL-10 and TNFα were provided but indicate no clear relation throughout treatment.

ADA

Of the 4 LBCL subjects who were ADA positive on treatment (but not at baseline), 2 subjects discontinued treatment within the first 2 cycles due to PD, and the other 2 subjects had a BOR of CR as assessed by IRC and remained on treatment for more than 10 cycles after testing ADA-positive.

- **Summary of main efficacy results**

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 30: Summary of efficacy for trial GCT3013-01

Title: A Phase 1/2, Open-label, Dose Escalation Trial of GEN3013 in Patients With Relapsed, Progressive or Refractory B-Cell Lymphoma		
Study identifier		GCT3013-01 (EPCORE™ NHL-1), 2017-001748-36, NCT03625037
Design		Open-label, multicenter, phase 1/2 single arm trial of epcoritamab in subjects with relapsed, progressive, or refractory B-cell lymphoma. The trial includes 2 parts: a Dose Escalation Part and an Expansion Part. The Expansion Part consists of 3 cohorts enrolling aggressive B-cell non-Hodgkin lymphoma (aNHL*), indolent B-cell non-Hodgkin lymphoma (iNHL) and mantle cell lymphoma (MCL) separately. The aNHL* cohort is the pivotal cohort for this submission.
	Duration of main phase: Duration of Run-in/ extension phase:	Initiation date (Expansion Part): 19 Jun 2020. The study is currently ongoing; clinical cut-off date 31 January 2022. not applicable
Hypothesis		No formal statistical hypotheses were formulated in this trial.
Treatments groups	Expansion Part aNHL Cohort: aNHL* patients after two or more lines of systemic therapy	aNHL Cohort There were N=139 patients with DLBCL and N=18 patients with other LBCL. Treatment Epcoritamab was administered by SC injection in treatment cycles of 4 weeks, ie, 28 days. The RP2D regimen of epcoritamab, which included a priming dose of 0.16 mg (C1D1), an intermediate dose of 0.8 mg (C1D8), and a full dose of 48 mg (C1D15, C1D22, and thereafter), was administered according to the following schedule: ☐ Cycles 1 to 3: Days 1, 8, 15, and 22 (QW) ☐ Cycles 4 to 9: Days 1 and 15 (Q2W) ☐ Cycle 10 and beyond until unacceptable toxicity, PD, or withdrawal of consent: Day 1 (Q4W)

Endpoints and definitions	Primary endpoint	Primary analysis was based on IRC-assessed ORR determined by Lugano criteria (Cheson et al., 2014). The BOR prior to initiation of subsequent anti-lymphoma therapy per response criteria was summarized.
	Key Secondary endpoints	Duration of response (DOR; by Lugano criteria as assessed by IRC) was defined as the time from the first documentation of response to the date of PD or death
		The Complete response (CR) rate was defined as the proportion of subjects with BOR of CR by Lugano criteria as assessed by IRC.
		Duration of complete response (DOCR) was defined as the time from the first documentation of CR to the date of PD or death, whichever occurred earlier, among all subjects reaching CR by Lugano criteria as assessed by IRC.
		Progression-free survival (PFS) was defined as the time from C1D1 to date of PD or death due to any cause, whichever occurred earlier. Date of PD was defined as the earliest date of documented progression after which there was no more PR or CR assessment. Analysis based on response assessment by Lugano criteria as assessed by IRC.
		Time to response (TTR) was defined as the time from C1D1 to first documentation of objective tumor response (PR or better) among all responders. Analysis based on response assessment by Lugano criteria as assessed by IRC.
		Overall survival (OS) was defined as the time from C1D1 to death from any cause. If a subject was not known to have died, then OS was censored at the latest date the subject was known to be alive. Survival status was to be assessed at least every 3 months after last administration of epcoritamab and to continue until the subject died or withdrew from the trial.
		Time to next (anti-lymphoma) therapy (TTNT) was defined as the time from C1D1 to first recorded administration of subsequent anti-lymphoma therapy with curative intent or death, whichever occurred earlier. Subject death due to disease progression was considered an event. Death due to other reasons was censored at the death date.
		MRD negativity is defined as no malignant clone sequence being detected at a given threshold in PBMCs (for 10-5, the clone sequence is not detected in the background of 100,000 nucleated cells).

Clinical Cutoff Date		31 January 2022	
	Results and Analysis		
Analysis description	**Primary Analysis**		
Analysis population and time point description	The population for efficacy analysis is the FAS: all subjects who received at least 1 dose of epcoritamab. Results were also provided for the DLBCL subgroup. MRD was evaluated in all subjects in the FAS who had at least 1 baseline or on treatment MRD sample and were either MRD positive or not evaluated at baseline. As of the data cutoff date, median duration of follow up was 11.0 months (range: 0.3, 17.9) for subjects with DLBCL		
Descriptive statistics and estimate variability	Treatment group	**GCT3013-01 Expansion Part, aNHL Cohort** **LBCL (N=157)**	**GCT3013-01 Expansion Part, aNHL Cohort** **DLBCL subgroup (N=139; requested indication)**
	Best Overall Response (by IRC), n (%)	99 (63.1%)	86 (61.9%)
	95% CI[2]	55.0, 70.6	53.3, 70.0
	Median DOR (by IRC), months	12.0	12.0
	95% CI	6.6, NR	6.6, NR
	CR (by IRC), n (%)	61 (38.9%)	54 (38.8%)
	95% CI[2]	31.2, 46.9	(30.7, 47.5)
	Median DOCR (by IRC), months	12	12
	95% CI	9.7, NR	9.7, NR
	PFS (by IRC), median (95% CI)[3], months	4.4 (3.0, 8.2)	4.4 (3.0, 8.2)
	TTR (by IRC), median (range), months	1.4 (1.0, 8.4)	1.4 (1.0, 8.4)
	OS, median (95% CI)[3], months	NR (11.3, NR)	NR (11.3, NR)
	TTNT, median (95% CI)[3], months	7.4 (5.9, 10.8)	8.2 (6.0, 13.9)
	MRD negativity	37/55 (67.3%, 95CI 53.3%, 79.3%)	32/47 (68.1% 95% CI 52.9%, 80.9%
Effect estimate per comparison	Not applicable, single-arm study.		

Notes	ORR, CR, PFS, DOR, DOCR, TTR determined by LYRIC as assessed by IRC and Changes in lymphoma symptoms as measured by the FACT-Lym were also secondary efficacy endpoints but are not shown here. [2] Based on the Clopper and Pearson method. [3] Based on Kaplan-Meier estimate.

2.6.5.3. Clinical studies in special populations

The applicant has summarized the number of elderly patients in GCT3013-01 (expansion) by age group (65 to < 75, 75 to < 85, ≥ 85 years) in Table 44.

Table 31: Age Categories (48 mg Dose-Studies GCT3013-01 and GCT3013-04 Safety Analysis Set)

	GCT3013-01 ESC+EXP		GCT3013-01+GCT3013-04 ESC+EXP		
	R/R LBCL (N = 167)	R/R DLBCL (N = 148)	R/R LBCL (N = 208)	R/R DLBCL (N = 188)	ALL B-NHL (N = 374)
Age at informed consent					
< 65 years	83 (49.7%)	68 (45.9%)	96 (46.2%)	80 (42.6%)	157 (42.0%)
65 to < 75 years	53 (31.7%)	49 (33.1%)	73 (35.1%)	69 (36.7%)	144 (38.5%)
75 to < 85 years	31 (18.6%)	31 (20.9%)	38 (18.3%)	38 (20.2%)	70 (18.7%)
≥ 85 years	0	0	1 (0.5%)	1 (0.5%)	3 (0.8%)

B-NHL = B-cell non-Hodgkin lymphoma; DLBCL = diffuse large B-cell lymphoma; ESC = escalation; EXP = expansion; LBCL = large B-cell lymphoma; R/R = relapsed or refractory

Note: Percentages calculated based on N.

2.6.5.4. In vitro biomarker test for patient selection for efficacy

2.6.5.5. Analysis performed across trials (pooled analyses and meta-analysis)

N/A

2.6.5.6. Supportive study(ies)

The applicant has presented the DLBCL expansion cohort (N=36) of the GCT3013-04 phase 1/2 clinical trial in Japanese subjects with R/R B-NHL, as a supportive study. This is an open-label, single-country, interventional, multicohort, phase 1/2 trial in Japanese subjects with R/R B-NHL. The trial consists of 2 parts: a Dose Escalation Part and an Expansion Part. Treatment in the expansion part was the same

as in the pivotal GCT3013-01 trial. The Monotherapy Expansion Part of the trial was conducted in 2 cohorts of subjects with R/R DLBCL or FL patients. The eligibility criteria were comparable to the GCT3013-01 trial except that patients were to be of Asian race and Japanese ethnicity. In the DLBCL cohort, patients with DLBCL, including DLBCL DH/TH disease (formally HGBCL with MYC and BCL2 and/or BCL6 according to the 2016 WHO classifications), were recruited.

As of the data cutoff date of 31 Jan 2022, a total of 36 subjects were enrolled and received ≥1 dose of epcoritamab in the DLBCL expansion cohort. In total 19 (52.8%) patients were female. The median age was 68.5 years (range: 44, 89). Most subjects had a baseline ECOG performance status of 0 (58.3%) or 1 (36.1%). Subjects who had not received a prior ASCT were required to be ineligible for transplant; reasons for ineligibility included age (66.7%), ECOG performance status (2.8%), prior transplant (16.7%), and other (13.9%; ie, lymphoma in peripheral blood, refractory, resistant or refractory to chemotherapy, and not applicable). The median number of prior lines of anti-lymphoma therapy was 3.0 (range: 2, 8), with 44.4% having received 2 prior lines of therapy, 25.0% having received 3 prior lines of therapy and 30.6% having received ≥4 prior lines of therapy.

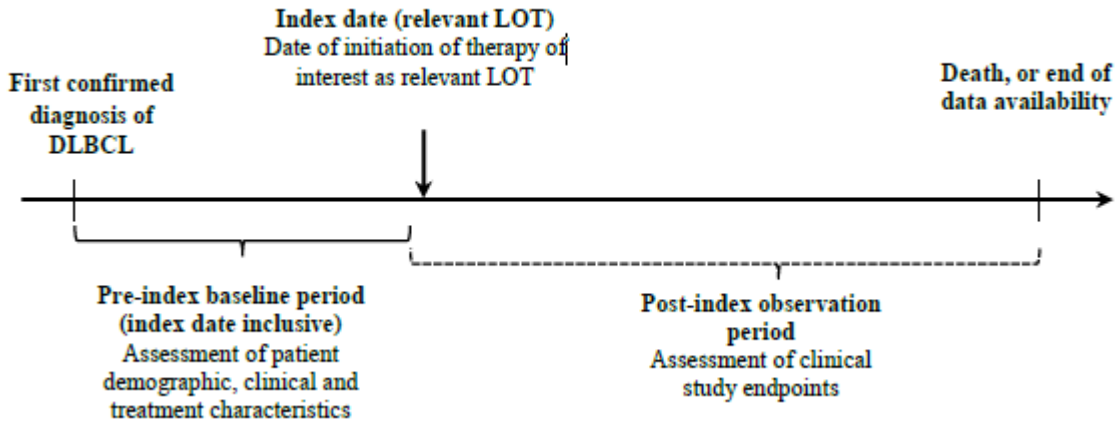
As of the data cutoff date of 31 Jan 2022, the median duration of follow up was 8.4 months (range: 1.5, 12.0) for the DLBCL expansion cohort. Based on IRC assessment determined by Lugano criteria, the ORR (CR + PR) was 55.6% (95% CI: 38.1, 72.1). The CR rate was 44.4% (95% CI: 27.9, 61.9). Based on IRC assessment, the median DOR was not reached. The estimated percentage of subjects remaining in response at 6 months was 69.3% (all responders) and at 9 months was 59.4% (all responders); for those achieving CR, 61.9% remained in CR at both 6 and 9 months. The median PFS was 4.1 months (95% CI: 1.2, not reached). The median OS was not reached. The estimated percentage of subjects who remained alive at 9 months was 59.8% (95% CI: 38.5, 75.8).

Real word evidence study

The applicant provided a real word evidence (retrospective cohort) study to characterize the ORR, CR and DOR among patients with R/R DLBCL treated with chemotherapy, single agent rituximab/obinutuzumab, single-agent lenalidomide, or combinations of these agents in the R/R treatment setting. Other time to event endpoints were also collected but these are not reflected here.

This retrospective observational study was conducted using data from multiple clinical centers (academic, for-profit, community, and hospital systems) in the US and housed in the COTA EHR database. Longitudinal patient-level data were used to describe clinical endpoints and patient characteristics. The design of the study is displayed in Figure 25.

Figure 19: Study Design real word data study



The index date for a given line of treatment was defined as the initiation date of the first treatment for each relevant line of treatment. To characterize each specific line of treatment, patients' demographic and baseline clinical characteristics were assessed during the pre-index period. When multiple observations of the demographic or clinical characteristics were available, the observation closest to the index date was used.

The overall COTA EHR database included an estimated 5,000 adult patients with DLBCL with a treatment record and diagnosis between January 1, 1994 to March 31, 2022. Patients selected for this analysis had a record of treatment and diagnosis of DLBCL between 01 January 2010 and March 31st 2022. A diagnosis of DLBCL was based on a record of pathological confirmation of an initial DLBCL diagnosis. Some main eligibility criteria were comparable to the pivotal study, however patients in this study had R/R disease previously treated with ≥1 line of systemic therapy instead of 2 lines and patients in this study did not have to be ineligible to HSCT/had received prior HSCT contrary to the pivotal study.

The total number of patients treated with a regimen of interest in the R/R treatment setting (i.e., with ≥1 prior line of treatment) and included in the study was 573; of these, 179 (31.1%) patients had ≥2 prior lines of treatment, and 77 patients (13.4%) ≥3 and 35 (6.1%) ≥4. The year of diagnosis was between2010-2015 for 52.5% and between 2016-2021 for 47.5% of the patients.

Baseline characteristics of the real-world study population differed from the pivotal study population among others in less lines of treatment, more ECOG 2 patients, lower IPI scores, and different types of prior therapies compared to the pivotal study population.

In the real-world study population (ie, patients with ≥1 prior LOT, N=573); the ORR was 52% (95% CI:48%-56%), the CR rate was 23% (95% CI: 19%-27%). In the subgroup of patients with ≥2 prior lines of therapy (n=179); the ORR and CR rate were 40% (95% CI: 33%- 48%) and 13% (95% CI: 8%-19%), respectively. The DOR and DOCR in the overall study population (i.e., patients with ≥1 prior LOT) were 3.5 (95%CI:3.0-4.7) months and 18.4 (95%CI:11.8-32.7) months, respectively. In the subgroup of patients with ≥2 prior lines of therapy these numbers were 2.7 (95%CI: 1.9-3.4) months and 9.6 (95%CI: 4.9-28) months, respectively.

Limitations to this study as indicated in the report are amongst others, differences in tumor response data or the timing of response assessment, the use of COTA's proprietary algorithm to define what constituted a line of treatment may differ from a physicians intentions. Incomplete records and documentation of information, variability in the quality of information recorded by physicians, difficulty verifying information found in the database, and differences in clinical practices across study sites are also limitations. Finally, the study findings may not be generalizable to the general patient population with R/R DLBCL in the US.

Comparison with available therapies in the context of CMA

A side-by-side comparison of the patient population and efficacy for epcoritamab and currently available treatments for R/R DLBCL in the EU is shown in Table **45: Patient Population and Efficacy Comparison for Epcoritamab and Currently Available Treatments for R/R DLBCL in the European Union**. A summary of the applicant's justification of the MTA over existing methods justification is provided in Table 46.

Table 32: Patient Population and Efficacy Comparison for Epcoritamab and Currently Available Treatments for R/R DLBCL in the European Union

Drug Name (Trade Name, if Available)	Epcoritamab[a]	R-GemOx[b]	BR[c]	Pixuvri[d]	Yescarta[f]	Kymriah[g]	Breyanzi[h]	Polivy + BR[c]	Minjuvi+ len[e]	Zynlonta
Type of Approval	NA	NA	NA	full	full	full	full	full	CMA	CMA
Mechanism of Action	Bispecific antibody	mAb + chemo	mAb + chemo	chemo	CAR T-cell	CAR T-cell	CAR T-cell	ADC + mAb + chemo	mAb + immunomod	ADC
Route of Administration	SC	IV	IV	IV	IV	IV	IV	IV	IV	IV
Patient Population	RR after ≥2L, pts ineligible for ASCT or having failed prior ASCT			Multiply RR (3L&4L)	RR after ≥2L	RR after ≥2L & no available treatment life prolonging option i.e. HSCT	RR after ≥2L	RR who are not candidates for HSCT	RR who are not eligible for ASCT	RR after ≥2L
Full analysis set (N)	139 All treated	196	40	70	101 All treated	115 All treated	269 ITT	40 ITT	81 All treated	145 All treated
Number of prior LOT (%):										
1	0	58	30	0	2	4.3	3	27.5	49.4	0
2	29.5	23	22.5	45.7	29	44.3	45	27.5	43.2	43
3	33.8	NA	NA	NA	30	31.3	25	NA	6.2	24
>3	36.7	19	47.5	50	40	20	26	45	1.2	32
Prior ASCT therapy (%)	18.7	16	15	15.7	25	48.7	33	25	11.1	17
Prior CAR T-cell therapy (%)	38.1	0	0	0	0	0	0	0	0	9
Prior therapies (%):										
Primary refractory	59	NA	NA	NA	2	NA	NA	NA	18.5	20
Refractory to ≥ 2 LOT	74.8	NA	NA	NA	76	NA	44	NA	NA	NA
Refractory to last LOT	82	57	85	57.1	79	54.8	67	75	44.4	61
Efficacy Results										
Response evaluable set (N)	139	196	40	70	101	99	216	40	81	145
ORR %	61.9	NA	32.5	40	74	54.5	72.7	70	56.8	48.3
CR rate %	38.8	NA	20	15.7	54	41.4	53.2	57.5	39.5	24.8
Duration of response (months)	15.6	NA	4.1	NA	NE	NE	20.2	10.3	43.9	13.4
Median PFS (months)	4.4	5	2.0	5.3	NA	NA	6.8	7.6	NA	4.9
Median OS (months)	NR	10	4.7	10.2	25.8	11.1	21.1	12.4	31.6	9.5
EOT ORR%	NA	38	17.5	37.1	NA	NA	NA	47.5	NA	NA
EOT CR rate%	NA	33	17.5	11.4	NA	NA	NA	40.0	NA	NA

Abbreviations: ADC = antibody-drug conjugate; aNHL = aggressive non-Hodgkin lymphoma; ASCT = autologous stem cell transplant; axi-cel = axicabtagene ciloleucel; BR = bendamustine and rituximab; CAR T-cell = chimeric antigen receptor T-cell therapy; CMA = conditional marketing approval; CR = complete response; DLBCL = diffuse large B-cell lymphoma; EU = European Union; IRC = independent review committee; IWG = international working group; mAb = monoclonal antibody; NA = not available; NL = not listed; ORR = Overall response rate; R-GEMOX = rituximab, gemcitabine, and oxaliplatin; R/R = relapsed/refractory; tisa-cel = tisagenlecleucel.
Epcoritamab: from the primary analysis of the R/R DLBCL patients within the pivotal aNHL expansion cohort of GCT3013-01 Study (cutoff date: 31 January 2022). Responses were based on ORR and CR, as determined by IRC, Lugano response criteria .
R-GemOx: . ORR and CR were reported as end of treatment, according to IWG response criteria .
(Polivy SmPC, 2022) was used as a source for efficacy analysis. BR was used as a comparator in the pivotal study GO29365. CR rate (IRC assessed, modified Lugano response criteria .at end of treatment is the primary endpoint. ORR and CR rate, end of treatment ORR and DOR were based on investigator assessment and part of key secondary endpoints. Both OS and investigator-assessed PFS were exploratory endpoints which were not type 1 error controlled. Background patient population was obtained from the assessment report (https://www.ema.europa.eu/en/documents/assessment-report/polivy-epar-public-assessment-report_en.pdf).
Pixuvri SmPC was used as a source for efficacy analysis. Responses were reported as end of study and end of treatment ORR and confirmed CR, as assessed by an independent assessment panel of a radiologist, an oncologist, and a pathologist (Cheson et al, 1999). There were 6/10 (8/6%) subjects had CRu at EOT and End of Study. CR/Cru was 14 (40%) at EOT and 17 (24.3%) at EOT. Responses were based on a sample size of 70 patients in the aNHL cohort at which 53 patients (76%) were DLBCL. Background patient population was obtained from the assessment report (https://www.ema.europa.eu/en/documents/assessment-report/pixuvri-epar-public-assessment-report_en.pdf). In the assessment report, there were 3 (4.3%) subjects had ≥6 prior lines of therapy.
(Yescarta SmPC, 2022) was used as a source for efficacy analysis. Responses were reported at 24-month analysis with ORR and CR based on IRC based on Lugano response criteria . Efficacy was based on 101 patients with refractory LBCL, at which 76.2% (n=77) was DLBCL. Background patient population was obtained from the assessment report (https://www.ema.europa.eu/en/documents/assessment-report/yescarta-epar-public-assessment-report_en.pdf).
(Kymriah SmPC, 2022) was used as a source for efficacy analysis. Responses were based on best ORR and CR as determined by IRC, Lugano response criteria.
(Breyanzi SmPC, 2022) and were used as a source for efficacy analysis. Responses were based on best ORR and CR as determined by IRC, Lugano response criteria . Study was based on large B-cell lymphoma cohort (n=229) consisted of 117 patients (51.1%) DLBCL not otherwise specified, 60 patients (26.2%) DLBCL transformed from indolent lymphomas, 33 patients (14.4%) high-grade B-cell lymphoma with gene rearrangements in MYC and either BCL2 or BCL6 or both, 15 patients (6.6%) with primary mediastinal B-cell lymphoma, and 4 patients (1.8%) with FL grade 3B. Median PFS and OS were from . Background patient population was obtained from . For refractory ≥2 LOT, 119 (44%) subjects who had never achieved CR with previous therapy (not only primary refractory but also refractory to subsequent lines of treatment) and subjects needed at least 2 prior LOT to enter the study.
(Minjuvi SmPC, 2022) was used as a source for efficacy analysis. Responses were reported as best ORR and CR (at ≥35-month analysis; 30 Oct 2020 cut-off) as determined by IRC, according to 2007 IWG response criteria . Background patient population was obtained from the assessment report (Minjuvi Assessment Report, 2021).
Assessment Report (EMA/CHMP/834750/2022) for Zynlonta (loncastuximab tesirine) was used as a source for efficacy. Efficacy was evaluated on the basis of ORR, as determined by IRC, Lugano response criteria.[2]

Table 33: Summary of Major Therapeutic Advantage Over Existing Methods Justification

Drug Name (Trade Name, if Available)	Justification Supporting a Major Therapeutic Advantage of Epcoritamab
R-GemOx	monotherapy, novel MoA (chemo-free), improved efficacy, and improved safety profile
BR	monotherapy, novel MoA (chemo-free), improved efficacy, and improved safety profile
Pixuvri	novel MoA (chemo-free), improved efficacy, and improved safety profile
Polivy+BR	monotherapy, novel MoA (chemo-free), improved efficacy in poorer prognosis patients, and improved safety profile
Minjuvi+lenalidomide	monotherapy, novel MoA, improved efficacy in poorer prognosis patients, and improved safety profile
Yescarta	novel MoA (chemo-free), improved safety profile, and improved availability/ease of use
Kymriah	novel MoA (chemo-free), improved efficacy in poorer prognosis patients, improved safety profile, and improved availability/ease of use
Breyanzi	novel MoA (chemo-free), improved safety profile, and improved availability/ease of use

axi-cel = axicabtagene ciloleucel; BR = bendamustine and rituximab; DLBCL = diffuse large B-cell lymphoma; MoA = mechanism of action; R-GemOx = rituximab, gemcitabine, and oxaliplatin; R/R = relapsed/refractory; tisa-cel = tisagenlecleucel.

In response to the 1st LoQ the applicant provided additional data comparing polatuzumab vedotin in combination with BR (polatuzumab + BR) with epcoritamab (DCO: 30 June 2022), see Table 48. The efficacy and safety of polatuzumab vedotin in combination with BR (polatuzumab + BR) was evaluated in a pivotal, global, multicentre, open-label trial (GO29365) which included a randomized cohort of 80 subjects with previously treated DLBCL (40 subjects each in the polatuzumab + BR arm or BR arm), using results as publication by Sehn 2020 at a median follow-up of 37.6 months. In this article the IRC response assessment is used instead of investigator assessed ORR and longer follow up is provided compared to the data in the SmPC which was used for Table ***45***. See Table 47, Table 48 and Table 49.

Table 34: Patient Population of Subjects with DLBCL Enrolled in the GCT3013-01 Trial (Epcoritamab) vs GO29365 Trial (Polatuzumab + BR)

Treatment	**Epcoritamab[a]**	**Polatuzumab + BR[b]**
Full Analysis Set (N)	139	40
Age, median (range)	66 (22,83)	67 (33, 86)
Age ≥65 years (>75 years)	52.6 (20.9)	57.5 (NL)
Number of prior LOT (%)		
1	0	27.5
2	30.2	27.5
≥3 (3, >3)	69.8 (32.4, 37.4)	45 (NL, NL)
Prior ASCT therapy (%)	18.7	25
Prior CAR T-cell therapy (%)	38.1	0
Primary refractory (%)	59	NL
Refractory to ≥2 LOT (%)	74.8	NL
Refractory to last LOT (%)	82	75

ASCT = autologous stem cell transplant; BR = bendamustine and rituximab; CAR T-cell = chimeric antigen receptor T-cell therapy; DLBCL = diffuse large B-cell lymphoma; NL = not listed.

a. From the updated analysis of 139 subjects with DLBCL from the pivotal aNHL expansion cohort (n=157) of GCT3013-01 trial (clinical DCO: 30 June 2022). Source: T14.1.1.2, T14.1.1.6.1

b. Polatuzumab vedotin (Polivy) initial assessment report (EMA/CHMP/690748/2019) was used as a source for background patient population.

Table 35: Efficacy Analysis of Epcoritamab (Based on Updated 30 June 2022 DCO) vs Polatuzumab + BR in Subjects with DLBCL

Treatment	***Epcoritamab[a]*** ***N=139***	***Polatuzumab + BR[b]*** ***N=40***
Overall Response Rate[c] % (95% CI)[d]	*61.9 (53.3, 70.0)*	*62.5 (45.8, 72.3)*
Complete Response Rate % (95% CI)[d]	*38.8 (30.7, 47.5)*	*50.0 (34, 66)*

Duration of Response- all responders (PR+CR)

Median DOR, in months (95% CI)[e]	*15.6 (9.7, NR)*	*12.6 (7.2, NE)*
Median DOR follow-up, in months (95% CI)[f]	*9.9 (9.7, 13.2)*	*NL*
Estimated percentage of subjects remaining in response (95% CI)[e]		
6-month	*66.5 (55.0, 75.7)*	*NL*
9-month	*63.6 (51.9, 73.2)*	*NL*
12-month	*57.2 (44.4, 68.1)*	*NL*
Duration of Response – in subjects with complete response		
Median, in months (95% CI)[e]	*17.3 (15.6, NR)*	*NL*
Median follow-up, in months (95% CI)[f]	*10.1 (9.7, 13.8)*	*NL*
Estimate percentage of subjects remaining in response (95% CI)[e]		
6-month	*92.1% (80.4, 97.0)*	*NL*
9-month	*89.9% (77.3, 95.7)*	*NL*
12-month	*80.1% (62.8, 90.0)*	*NL*
Median PFS, in months (95% CI)[e]	*4.4 (3.0, 8.8)*	*9.5 (6.2, 13.9)*
Median OS, in months (95% CI)[e]	*18.5 (11.7, NR)*	*12.4 (9.0, NE)*

BR = bendamustine and rituximab; DLBCL = diffuse large B-cell lymphoma; DOR = duration of response; IRC = independent review committee assessed; NE = not estimable; NL = not listed; ORR = Overall response rate; OS = overall survival; PFS = progression-free response; R/R = relapsed/refractory.

a. From the updated analysis of 139 subjects with DLBCL from the pivotal aNHL expansion cohort (n=157) of GCT3013-01 Study (clinical DCO: 30 June 2022). Responses were based on ORR and CR, as determined by IRC, Lugano response criteria. [2]. Source: T14.2.1.1.1, T14.2.1.7.1, T14.2.1.11.1, T14.2.1.12.1, 14.2.1.17

b. Source: Sehn, 2020[6] for Best Response (IRC assessed, Lugano, 2014 criteria)[2] including objective response and complete response. Polatuzumab vedotin (Polivy) initial assessment report (EMA/CHMP/690748/2019) was used as a source for the other efficacy analysis (DOR, PFS IRC assessed, Lugano, 2014).[2]

c. ORR= CR+ PR

d. Based on the Clopper-Pearson method

e. Based on Kaplan-Meier estimate

f. Based on reverse Kaplan-Meier estimate

Table 36: Best Overall Response for Subjects with DLBCL with 2 or More Prior LOT

Population	Epcoritamab[a]			Polatuzumab + BR[b]		
	N	Best Response, IRC assessed		N	Best Response, IRC assessed	
		ORR	CRR		ORR	CRR
Subjects without prior CAR T-cell therapy	86	67%	42%	102	50%	42%
Subjects with prior CAR T-cell therapy	53	53%	34%	0	NA	NA

BR = bendamustine and rituximab; CAR T= chimeric antigen T-cell therapy; CRR = complete response rate; IRC= independent review committee; ORR = overall response rate; NA = not available.

a. From subgroup analysis of 139 subjects with DLBCL from the pivotal aNHL expansion cohort (n=157) of GCT3013-01 trial, (clinical DCO: 30 June 2022). Source: F14.2.1.1.1, F14.2.1.2.1

b. Source: Best response rates of subjects with DLBCL with 2 or more prior LOT (n=102) from the pooled population of polatuzumab + BR extension cohort (n=106).[7] There is one subject who received prior CAR T-cell therapy in the pooled extension cohort, but it is unclear whether that subject is part of the 102 subjects with 2 or more prior LOT with best overall response.

At the request of the CHMP the applicant provided additional data comparing Columvi (glofitamab) with epcoritamab. Glofitamab is a CD20-CD3 T-cell engaging, bispecific antibody, for the treatment of adult patients with R/R DLBCL, after 2 or more lines of systemic therapy and received a positive CHMP opinion and EC decision for a CMA within this procedure. To demonstrate that epcoritamab addresses the unmet medical need to at least a similar extent to glofitamab, the applicant has conducted a cross-trial comparison. Baseline disease characteristics were largely comparable between the GCT3013-01 (epcoritamab) and NP30179 (glofitamab) trials.

Table 37: **Efficacy Comparison of Epcoritamab vs Glofitamab in Subjects**

Drug Name	Epcoritamab[a] (N=139)	Glofitamab[b] (N=155)
Overall Response Rate[c] % (95% CI)[d]	61.9 (53.3, 70.0)	52 (43, 60)
Complete Response Rate % (95% CI)[d]	38.8 (30.7, 47.5)	39 (32, 48)
Duration of Response (DOR)– all responders (PR+CR)		
Median DOR, in months (95% CI)[e]	15.6 (9.7, NR)	18.4 (13.7, NR)
Median DOR follow-up, in months (95% CI)[f]	9.9 (9.7, 13.2)	10.6 (0, 21)
Estimate percentage of subjects remaining in response (95% CI)[e]		
6-month	66.5 (55.0, 75.7)	NL
9-month	63.6 (51.9, 73.2)	NL
12-month	57.2 (44.4, 68.1)	63.6 (51, 76)
Duration of Complete Response		
Median, in months (95% CI)[e]	NR (14.3, NR)	NR (16.8, NR)
Median follow-up, in months (95% CI)[f]	9.7 (8.4, 12.1)	10.6 (0, 21)
Estimate percentage of subjects remaining in response (95% CI)[e]		
6-month	91.2 (78.1, 96.6)	
9-month	88.6 (74.6, 95.1)	
12-month	71.8 (50.9, 84.9)	77.6 (64, 91)
Median PFS in months (95% CI)[e]	4.4 (3.0, 8.8)	4.9 (3.4, 8.1)
Median OS in months (95% CI)[e]	18.5 (11.7, NR)	11.5 (7.9, 15.7)[g]

CI = confidence interval; DLBCL = diffuse large B-cell lymphoma; NE = not evaluable; NL = not listed; NR = not reached; OS = overall survival; PFS = progression-free response; PR = partial response.
a. From the updated analysis of 139 subjects with DLBCL from the pivotal aNHL expansion cohort (n=157) of GCT3013-01 trial (clinical DCO: 30 June 2022) Responses were based on ORR and CR, as determined by IRC,Lugano response criteria 2. Source: T14.2.1.1.1, T14.2.1.7.1, T14.2.1.11.1, T14.2.1.12.1, 14.2.1.17
b. From 1, assessment according to IRC
c. ORR = CR + PR
d. Based on the Clopper and Pearson method
e. Based on Kaplan Meier estimate
f. Based on reverse Kaplan-Meier estimate
g. based on investigator assessment.

MAIC Analysis of Epcoritamab vs Glofitamab

Unanchored matching adjusted indirect treatment comparisons (MAIC) were conducted to estimate the comparative efficacy of epcoritamab for the treatment of R/R DLBCL (in patients with at least 2 prior LOT) from the GCT3013-01 trial vs the glofitamab NP30179 trial. As the subject populations of both trials are similar, with both trials including subjects with prior CAR T therapy 1, all 139 subjects within the GCT3013-01 trial were included in the comparison: subject-level data from the GCT3013-01 trial (epcoritamab) and published data from the glofitamab NP30179 trial.

Following minor adjustments in the baseline characteristics, including age, sex, disease stage, prior CAR T, primary refractoriness, ECOG status, prior ASCT, and refractoriness to the last anti-CD20 agent, an effective sample size of 127 subjects from the GCT3013-01 trial was compared to the 154 subjects in the NP30179 trial. The unadjusted and adjusted ORR were 61.9% and 61.9%, respectively with epcoritamab and 51.6% with glofitamab (p = 0.0761 and p = 0.075, respectively).

The unadjusted and adjusted CRR were comparable between epcoritamab (38.3% and 38.4%) and glofitamab (39.6%) (p = 0.929 and p = 0.863, respectively).

Subjects treated with epcoritamab vs glofitamab showed comparable OS, with HR = 0.798 in the unadjusted population (p = 0.188) and HR = 0.803 in the adjusted population (p = 0.209) and had comparable PFS.

2.6.6. Discussion on clinical efficacy

Design and conduct of clinical studies

The pivotal study population in this application is the aNHL cohort of the expansion phase of the GCT3013-01 study. The escalation phase of this study was used for dose finding. The DLBCL cohort of the GCT3013-04 study in Japanese subjects and a real world evidence study are presented as supportive studies.

GCT3013-01 study is an FIH, phase 1/2, single arm trial in subjects aged 18 years or older who had relapsed, progressive and/or refractory mature B-cell lymphoma including an expansion part with a (so-called) aNHL cohort, an iNHL cohort and a MCL cohort. The expansion part of the aNHL cohort, also referred to as LBCL cohort, is considered to be the pivotal study. In general the design is considered appropriate for an exploratory study. However, the single arm trial design introduces inherent limitations as the therapeutic effect might be subject to various sources of bias. In addition, efficacy may be overestimated in such a study design. Therefore, the results should be interpreted with caution. The incidence of LBCL/DLBCL may have allowed for an (underpowered) comparative trial, however, this application is interpreted in light of the CMA requested by the applicant. Scientific advice (EMEA/H/SA/4478/2/2020/III) was requested for the pivotal study and proposed confirmatory study. The applicant largely adhered to the advice.

There is no hypothesis or otherwise a-priori specification of success criterion for the primary endpoint as is expected of a clinical trial submitted as pivotal evidence for MA (ICH E9 Statistical Principles for Clinical Trials, CPMP/ICH/363/96). The applicant states hypotheses for sample size calculation, but they are not carried on as success criteria under statistical methods. Moreover, the hypotheses were criticised in SA (EMEA/H/SA/4478/2/2020/III) for being less conservative than e.g. the one selected for tisagenlecleucel (Kymriah). As such, the sample size hypotheses are not adequate in defining success in the sought therapeutic context. The applicant received scientific advice (EMEA/H/SA/4478/2/2020/III) where challenges for undertaking a two-arm trial was acknowledged, but it was stated that even an underpowered RCT would have been preferable. No statistical hypothesis or clear success criterion was prespecified for the primary endpoint, as is expected of clinical trials submitted as pivotal evidence for an MA.

A study population of certain LBCL types namely DLBCL patients plus ≤30 patients with PMBCL, HGBL and FL3B with relapsed or refractory (R/R) disease after at least 2 lines of systemic therapy including at least 1 anti-CD20 monoclonal antibody-containing therapy were included. CD20-positivity was based on a representative pathology report but histopathological testing to confirm CD20-positive DLBCL was not requested. This is considered unfortunate considering the nature of therapy and the fact that patients may be CD20 negative after having received anti CD20 therapy. Patients measured CD20 negative during the study were therefore not reported as protocol violations. According to the inclusion criteria (as specified in amendment 7), patients with DH/TH DLBCL (technically HGBL with *MYC* and *BCL2* and/or *BCL6* rearrangements according to the 2016 WHO classification), were also included in the DLBCL group. Patients needed to either have failed prior HSCT, or be ineligible for autologous HSCT. The eligibility criteria are considered appropriate to select the target population and thus considered acceptable.

The posology was investigated in the escalation part of the GCT3013-01 study (see below) and premedication/CRS prophylaxis consisted of prednisolone, diphenhydramine and acetaminophen. This

is adequately reflected by section 4.2 in the SmPC. Epcoritamab is to be given until unacceptable toxicity, PD, or withdrawal of consent. No adequate justification for continued treatment in those responding to therapy is provided. As the continued dosing was part of the studied regimen, it will not be possible to propose another regimen without clinical data. During the Expansion Part of the GCT3013-01 and GCT3013-04 trials some subjects have received epcoritamab drug product manufactured with the 2 different processes.

The primary endpoint of the study is ORR, which is considered an objective measure of tumour burden and an appropriate endpoint in a single-arm trial, if supported by DoR, which is included as a secondary endpoint in the study. It is noted that the ORR, CRR, DoR and DoCR reported includes patients who achieved PR/CR following previous PD (by Lugano) or IR (by LYRIC). The inclusion of these patients is acceptable, as it is thought to be reflective of pseudo-progression or delayed response upon start of epcoritamab therapy. This is also reflected in the SmPC section 5.1. For the response evaluations after 24 weeks, the time between assessments is increased from every 6 weeks to every 12 weeks. Because the true time of progression between the two timepoints is unknown, a long period between assessments may bias the estimated duration of response upwards. Sensitivity analyses were provided to evaluate the extent of any bias due to interval censoring, the results from these suggest that the results are not overly influenced by the longer period between assessments. The single arm-nature of study GCT3013-01 means that in particular time-to-event endpoints such as PFS and OS should be interpreted with caution.

The study was separated in two stages, with an interim analyses to be performed when approximately 25 patients with DLBCL had sufficient data (up to 12 weeks of follow-up) to be evaluable for response. The study was to proceed if more than seven patients had an ORR based on investigator assessment. The results for ORR and DoR were provided separately for Stage 1 and 2, with separate results also for those patients reported in the interim analyses report. The ORR is comparable between the stage 1 and stage 2 cohorts for the IRC assessment. This provides reassurance that the decision to continue the study was not based on over-optimistic early results and that the patient population was similar in both stages. The sample size for Stage 2 is prespecified for DLBCL only and this sample size was increased by 8% after interim analysis. The sample size of the other subtypes of aNHL than DLBCL is small and makes it challenging to evaluate treatment effect across these other subtypes. The results for the full aNHL cohort are therefore driven by DLBCL.

The amendments and deviations are not expected to have a significant impact on the study, however it should be noted that the amendments on the design of the expansion part were made while the escalation part was going, thus with possible knowledge of the outcomes. Thus, a data driven design of the expansion phase cannot be excluded. The last protocol amendment for the expansion part took place after the first subject signed informed consent for the expansion part. Amendment 7 was dated 23-Sep-2020, which is after the date at which the first subject signed informed consent (19-Jun-2020). Some patients had likely already been enrolled at the time of protocol amendment 7, as the data monitoring committee noted that on Oct-19-2020, 31 aNHL patients had been enrolled, 13 patients were in screening and 13 patients had had screening failures. In light of the exploratory nature of the study and the request for CMA, this is considered acceptable.

The dose escalation part of study GCT3013-01 was used for dose finding. In general, the design of this study is considered acceptable, however there are some issues identified. Determining of the optimal biological dose rather than determining the MTD would have been preferred, moreover the design and sample size do not allow to compare all the different posologies. There is some evidence from non-clinical and clinical E-R data from the dose escalation study supporting the rationale for a type of step up dosing, as well as relevant literature from other bispecific antibodies indicating that the use of step up dosing would reduce CRS, however such data to directly confirm this are missing as CRS rates without priming/intermediate dosing are not known. Considering that this regimen was used in the

pivotal clinical study this issue is not pursued. A dose optimisation cohort of Study GCT3013 01 is to investigate a different step up regimen in addition to hydration recommendations in DLBCL patients.

Based on PD and efficacy doses between 12 mg and 60 mg would have been acceptable. The occurrence of CRS is numerically higher in the 24 mg group (reason for this is not understood), but more or less comparable between the other doses between 12-60 mg. The applicant stated that the posology was selected based on modeling of the CRS rates, however this is not evident from the safety data alone. Therefore, the choice of 0.16 mg/0.8 mg/48 mg as the RP2D based on the available safety is not objected, however it is uncertain whether the most optimal dose has been selected. Of note, no formal dose response study was conducted.

In addition, during the study strategies to mitigate CRS were amended from cohort 7 onwards and again for the expansion cohort. It does appear that less CRS events were seen starting from cohort 7 compared to the previous cohorts, however this may also be influenced by changes in (step) up dose. Some support for the pivotal study may also derive from this study in terms of efficacy, but it should be considered that different B-NHL patients were included in the study and different posologies were used.

A routine GCP inspection has been performed for the escalation part of the GCT3013-01 study (EMA/IN/0000118168). Inconsistencies regarding the safety listings and the registration of AEs were identified (see Clinical Safety discussion). An update of the CSR is requested post-authorisation (see Annex II). In general the conduct of the escalation part of the GCT3013-01 clinical trial was not fully ICH-GCP compliant, based on the critical and major deviations mentioned in the integrated inspection report. The observed findings, however, were unlikely to have a significant impact on data integrity within the inspected escalation part of the GCT3013-01 clinical trial according to the inspectors. The inspection team did not identify any restrictions on the usability of the reported trial data and consider that the data of the escalation part of the GCT3013-01 clinical trial, as reported in the corresponding CSR, can be used for evaluation and assessment of the application. The escalation part of GCT3013-01 clinical trial is still considered to be conducted within internationally accepted ethical standards. The responses to the inspection report including the timely implementations of the actions for ongoing (if applicable) and future clinical studies, as set out in the CAPA plan, will further enhance the quality of clinical trials performed by Genmab (see also discussion on Clinical Safety).

Efficacy data and additional analyses

As of the data cutoff date of 31 Jan 2022, a total of 219 subjects were screened. In total 157 subjects received at least one dose of epcoritamab in the aNHL expansion cohort and 62 (28.3%) patients were screen failures and thus the FAS may be considered similar to the ITT in this study. In total, 13 subjects did not meet the inclusion criterion 2.a.i.1, according to Amendment 7 (CD20+ DLBCL per WHO 2016 or 2008 classification). The applicant did not collect details on the pathology report. This means that patients did not have a CD20+ biopsy, or that diagnosis was found to be a disease entity other than DLBCL (de novo/transformed) and DH/TH HGBL (prior to opening of stage 2). This is not further pursued considering the requested indication.

The trial is ongoing and the date of last observation for last subject recorded as part of the database for this analysis has not yet been reached.

The baseline data reflect a R/R LBCL population after multiple systemic therapies (at least 2); 29.3% had 2 prior therapies, 31.8% had 3 prior therapies and 38.9% had 4 or more prior therapies. In total 88.5% (N=139) DLBCL patients, 5.7% (N=9) HGBL patients, 2.5% (N=4) PMBCL patients and 3.2% (N=5) FL3B patients are included (by local laboratory). However, the DLBCL group included at least 16 patients with high-grade B-cell lymphoma (HGBL) with *MYC* and *BCL2* and/or *BCL6* rearrangements

(according to the 2016 WHO classification; see below). Despite that most patients were ineligible for ASCT very few patients with ECOG 2 were included. Incorrect identification of patients having prior transplant was found at one site. The applicant clarified that no additional misunderstandings of this nature occurred.

The median duration of follow-up was 10.7 months (range: 0.3, 17.9) for patients with LBCL and 11.0 months (range: 0.3, 17.9) for patients with DLBCL. The primary endpoint ORR was 63.1% (95% CI: 55.0, 70.6) in LBCL patients with 38.9% (95%CI: 31.2, 46.9) of the patients in CR. In the subgroup of DLBCL patients these numbers are comparable with an ORR of 61.9% (95%CI: 53.3, 70.0) and CR rate of 38.8% (95%CI: 30.7, 47.5). The median DOR was 12.0 months (95% CI: 6.6, NR) in LBCL and DLBCL patients. There is extensive censoring in the DoR curve. The majority of patients who were censored were censored due to "clinical cutoff", the applicant confirmed that these patients were alive, progression free and still actively in follow up at DCO. In the secondary censoring definition of DOR (according to treatment policy strategy) patients who received anti-cancer medication are continued to be followed up until progression or death (or censored at the DCO date). The estimated median DOR for the secondary definition is consistent with the estimated DOR for the primary definition (using the hypothetical strategy). In addition, the sensitivity analysis where start of new therapy is considered an event is a more conservative analysis, and as expected, a certain reduction in DOR, DOCR and PFS was observed. Overall, the provided sensitivity analyses support the robustness of the efficacy results provided.

The median DOCR was 12.0 months (95% CI: 9.7, NR) in LBLC and DLBCL patients. Acknowledging the uncertainties associated with the study design, the response rates in combination with the duration of response are considered to be clinically relevant and indicate anti-disease activity of epcoritamab in the study population. Updated efficacy analyses from a data cut-off (DCO: 30 June 2022; median study duration follow-up of 15.7 months) indicate similar response rates compared to the primary analyses. The median DOR in subjects with LBLC is 15.5 (9.7, NR) months and 15.6 months (95% CI: 9.7, NR) in DLBCL patients. The DOR for epcoritamab at the DCO date of 18 November 2022 is based on 86 DLBCL responders. The point estimate and the 95% confidence intervals for the median DOR are 15.5 months (9.7 months, 20.8 months).

No meaningful information is available regarding treatment of immunosuppressed patients. This information is adequately reflected in section 5.1 of the SmPC.

In the other LBCL entities response were seen in all five FL3B (3 patients in CR), in all four PMBCL patients (2 patients in CR) and in 44% (N=4/9) HGBL patients with 2 in CR. The DoR data from the other LBCL entities appear in range with the DoR from DLBCL patients.

Regarding FISH results at trial entry, 36 patients with DLBCL had local laboratory results to assess genetic rearrangements. Of these, 16 patients had *MYC*, *BCL2*, and/or *BCL6* rearrangements, classified as HGBCL with *MYC* and *BCL2* and/or *BCL6* rearrangements according to WHO 2016 criteria (Swerdlow et al., 2016). Based on central laboratory FISH analysis of screening tumor tissue available from 88 patients enrolled in the DLBCL cohort, 12 (13.6%) had tumors with *MYC*, *BCL2*, and/or *BCL6* rearrangements. Of the 51 subjects with DLBCL that did not have central FISH testing, 4 subjects had local FISH testing results indicating 2 were DH and 2 were TH. Combined with the above this indicates that DH/TH patients were among the DLBCL population. Among the 9 HGBCL subjects in the study, specimens from 4 HGBCL subjects were available for central FISH testing. Of these, 1 HGBCL subject was DH. Of the 5 HGBCL subjects without central FISH testing, 1 HGBCL subject had local FISH testing results of DH. In total, 18 subjects from the DLBCL and "other aggressive B-NHL" groups had DH/TH arrangement by either central or local FISH testing. Efficacy analysis based on central FISH results were performed post-hoc. The ORR (CR + PR) in subjects with DH/TH HGBL by central FISH (N=12) was 50.0% (95% CI: 21.1, 78.9), with 4 (33.3%) and 2 (16.7%) subjects achieving best response of

CR and PR, respectively. For subjects with DH/TH HGBCL by FISH (N=12), the median DOR among all responders was 12.0 months (95% CI: 1.1, NR). In the 18 subjects with DLBCL/HGBCL DH/TH lymphomas the ORR =50.0% [95% CI: 26.0, 74.0] and CRR=33.3% [95% CI: 13.3, 59.0)]. A slightly lower efficacy is observed in these patients compared to the LBCL population, which may be explained by the poorer prognosis in these patients. Nonetheless these numbers are considered clinically relevant.

Clinically relevant results have also been observed in patients with PMBCL, and FL3B disease. Although the number of patients within these disease entities were small, based on the MoA of epcoritamab and similarities in disease and biology from the LBCL entities to DLBCL, benefit could also be expected in these disease entities.

PFS and OS appear in support of the primary endpoint; the median PFS was 4.4 months (95%CI: 3.0, 7.9) in LBCL patients and 4.4 months (95%CI: 3.0, 8.2) in DLBCL patients. The median OS was NR (95%CI: 11.3, NR) in both LBCL and DLBCL patients. The other secondary endpoints (TTNT, TTR) also support the ORR. Time to response (TTR) was 1.4 months in the DLBCL population, which was close to first postbaseline disease assessment. Time to complete response (TTCR) was 2.7 months for DLBCL, which was close to the second postbaseline assessment. The results for this endpoint indicate a relatively rapid response, which is considered beneficial in a population with aggressive and rapidly progressing disease. It needs to be considered that time-dependent endpoints cannot be reliably assessed in single arm trials and that it is uncertain whether responses translate into OS benefit. As such confirmatory data is needed.

A total of 7 (4.5%) subjects received a subsequent allogeneic HSCT, and 1 (0.6%) subject received a subsequent ASCT. Each of these subjects had a BOR of PR (1 subject) or CR (7 subjects, including the subject who received ASCT) per IRC using Lugano criteria.

With regard to the exploratory analyses, PROs are difficult to interpret in a single arm trial. Of the 157 patients in the study, in total 146 (93.0%) were CD20 positive per local lab and N=8 (5.1%) of the patients were CD20 negative (level of expression of CD20<50%). All but one of these patients did not respond to treatment. Of note, the responding subject had an expression level of approximately 20% and expression of CD20 <20% as a cut-off was not discussed by the applicant. The applicant indicated that expression levels below 50% were observed in 8 out of 113 central immunohistochemistry (IHC) evaluable and response evaluable LBCL patients. All but one of these patients had PD as BOR. One patient had a PR as BOR. The label reports that there are limited data available on patients with CD20-negative DLBCL treated with epcoritamab and that these patients may have less benefit compared to patients with CD20-positive DLBCL. It was noted in subgroup analysis that DLBCL patients with less than median (5.1 months) time between the last dose of anti-CD20 therapy and the first dose of epcoritamab, had lower ORR (46%, 95%CI: 34, 59%) than those with longer than the median time (ORR 77%, 95%CI: 66, 86%). This cut-off is, however, arbitrary, and not clinically relevant. This variation can likely be attributed to different baseline disease characteristics and prior treatment history including shorter time from diagnosis to first dose, with more aggressive disease in the patient groups with poorer results. A comparison was requested of epcoritamab efficacy (ORR and CR-rate) in patients with low B-cell counts at baseline vs those with normal/increased B-cell counts (B-cell depletion in this instance acting as a surrogate marker of residual functional effects of prior anti-CD20 treatment). The responses observed in the subgroup of patients with low B-cell count (< 100 Cells/uL) were lower compared to those with normal/increase B-cell count (≥ 100 Cells/uL) at baseline. However the responses are still considered clinically relevant, and the subgroup with low B-cell count constituted the majority of the study population (126/139 DLBCL patients), thus restrictions on the indication based on B-cell counts are not considered justified based on these data.

GCT3013-04 is a phase 1/2 clinical trial in Japanese subjects with R/R B-NHL and the DLBCL cohort

(N=36) of this study is presented as an supportive study. In a similar population to the GCT3013-01 study the ORR based on IRC assessment by Lugano criteria was 55.6% (95% CI: 38.1, 72.1) with a CR rate of 44.4% (95% CI: 27.9, 61.9). The median DOR was not reached at a median follow up of 8.4 months. Thus, these data support the pivotal study. Real world study data was also provided as supportive evidence, however there were several limitations and uncertainties that limit the interpretation of these data, including differences in the pivotal study population and the real world study population, differences in timing of response analyses, the response criteria used and not including more recently approved therapies into the real world data set.

Additional efficacy data needed in the context of a conditional MA

The applicant has requested a conditional marketing approval. As stated, the single arm, dose escalation - expansion design introduces uncertainties to the observed therapeutic effect and confirmation of efficacy in the R/R DLBCL population is required for a full approval. The phase 3 GCT3013-05 trial is proposed as a confirmatory study. This ongoing trial compares treatment with epcoritamab to standard-of-care immunochemotherapy (i.e., R-GemOx or BR) in subjects with R/R DLBCL and HGBL, with the primary endpoint of OS. While the study population of the GCT3013-05 is not the same as the pivotal study population in terms of lines of treatment and included LBCL subtypes, the results of the GCT3013-05 study are considered to be relevant to confirm the B/R of the epcoritamab in the treatment of R/R DLBCL after two or more lines of systemic therapy. The design of this trial as a confirmatory study was considered acceptable in scientific advice (EMEA/H/SA/4478/2/2020/III) which is agreed. The applicant updated the sample size calculations, such as the expected HR and the number of events needed. With the updated design the applicant has mitigated some of the main concerns expressed by the CHMP at the time of scientific advice. Some concerns remain regarding the potential for inconclusive results, particularly in the subgroups. Given the open label nature of the study, it is also important to ensure that the treatment decisions of patients remaining in follow up will not be impacted by the interim results. A submission of a type II variation in the EU will take place after the final OS analysis (due date Q4 2024). A 5-year follow-up for safety is planned and will be part of the amended protocol. The applicant will provide the final CSR of study GCT3013-01, the pivotal study for this application, as specific obligation.

For the purpose to discuss the MTA the applicant provided an inter-trial comparison of efficacy and safety data. Limitations associated with inter-trial comparisons should be noted, particularly when there are (small) differences in study population and differences in methods to measure response duration. Compared to Minjuvi, Zynlonta and Columvi, available therapies with a CMA, comparable or higher ORR and CR rates are observed for epcoritamab, thus indicating that epcoritamab addresses the unmet medical need to at least a similar extent than Minjuvi, Zynlonta and Columvi. Compared to available therapies for the target population with a full approval, epcoritamab has numerically higher rates in terms of ORR and CR rate compared to R-Gem-OX, BR, Pixuvri and Kymriah, but numerically similar or lower rates in terms of ORR and CR rate compared to Yescarta and Breyanzi. However, an advantage of epcoritamab versus the CAR-T cell therapies Yescarta and Breyanzi is that epcoritamab is immediately available (off-the-shelf), and that epcoritamab does not require administration in a specialized centre. This is considered to constitute a MTA over the CAR T-cell therapies. Compared to Polivy+ BR in terms of ORR and CR rate it cannot be concluded that epcoritamab has numerically higher rates. When considering the median DOR cross study comparison seems to favor epcoritamab over polatuzumab + BR, but potential differences in analysis methods should be taken into account. Compared to polatuzumab + BR, epcoritamab has shown evidence of activity in patients who have failed prior CAR t cell therapy (CR/ORR/DoR) while polatuzumab + BR has yet to demonstrate effect in this setting. DOR results also appear to support an MTA. Therefore, it is considered that epcoritamab will provide meaningful clinical effects in patients with R/R DLBCL and thus constitute an additional treatment option in this non-curative 3L+ setting.

The applicant claims overcoming drug resistance associated with the current available therapies approved in the EU, but a population resistant to approved therapies was not explicitly targeted. The included population nonetheless included a substantial portion of patients refractory to their last line of therapy, as well as to specific defined therapies, such as CAR-T cell products. The applicant considers that that the patient population enrolled in the epcoritamab study (GCT3013-01) was more refractory, had higher risk, and poorer prognosis compared to other available therapies, however subgroups of these patients have also been included in clinical studies which led to approvals in the target population and therefore it cannot be stated that this justifies an MTA. The route of administration as subcutaneous (SC) is considered to be of ease by the applicant, however it is uncertain if this led to advantages for patients such as decreased hospitalisation, and reduced treatment burden and does not constitute a MTA.

2.6.7. Conclusions on the clinical efficacy

Clinically relevant responses and duration of response were observed in the study population of LBCL subtypes DLBCL NOS, HGBL, PMBCL as well as in FL3B who are R/R after two or more lines of systemic therapy.

The single arm trial phase 1/2 design introduces inherent limitations as the observed therapeutic effect might be subject to various sources of bias. In addition, efficacy may be overestimated in such a study design. Therefore, the results should be interpreted with caution and confirmation of efficacy in the R/R DLBCL population is required for a full approval.

The CHMP considers the following measures necessary to address the missing efficacy data in the context of a conditional MA:

- In order to confirm the safety and efficacy of epcoritamab in the treatment of R/R DLBCL after two or more lines of systemic therapy, the results of the primary (including final OS analysis) and final safety and efficacy analyses for study GCT3013-05 should be submitted.
- In order to confirm the safety and efficacy of epcoritamab in the treatment of R/R DLBCL after two or more lines of systemic therapy, the final CSR for study GCT3013-01 should be submitted.

The CHMP considers the following measures necessary to address issues related to efficacy:

- The provision of the updated CSR of GCT3013-01-ESC CSR (see Annex II).

The applicant accepted a recommendation from the CHMP to provide the results of a dose optimisation cohort of Study GCT3013-01 investigating a different step up regimen (0.32/1.6/48mg versus 0.16/0.8/48mg) in addition to hydration recommendations in DLBCL patients.

2.6.8. Clinical safety

Mechanism of action

Epcoritamab is a bispecific antibody recognizing the T-cell antigen CD3 and the B-cell antigen CD20. The mechanism of action of epcoritamab is induction of T cell-mediated killing of CD20-positive cells by co-engaging CD3 on T cells and CD20-expressing B cells. As a result, epcoritamab induces cytolytic synapse formation and kills CD20-positive target cells, independent of ligation of a peptide-MHC complex by the T cell receptor. Epcoritamab can induce cytotoxic activity in both CD4+ and CD8+ T-cells.

The safety profile of CD3-binding bispecific antibodies share features with that of CAR T-cells, both being T-cell-redirecting treatments associated with a risk of unique complications such as cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS) and tumour flare. However, adverse events commonly seen with conventional chemotherapy are also reported with bispecific antibodies including fatigue, cytopenias, infections, diarrhoea and elevated liver enzymes. Tumour lysis syndrome has also been reported (Salvaris et al., 2021).

Preclinical safety

Effects of epcoritamab observed in cynomolgus monkeys included cytokine release and consequent clinical signs (vomiting, hunched posture, subdued behaviour), depletion of peripheral blood B cells, and decreased lymphoid cellularity in lymphoid tissues. Slightly lower haemoglobin concentrations and haematocrits were also observed. The findings considered associated with elevated cytokine levels were observed primarily following the first dose (please refer to the non-clinical assessment).

In the current assessment safety data of epcoritamab in LBCL are presented from the pivotal Study GCT3013-01 and the supportive study GCT3013-04 (Table 51)

Table 38: Summary of Sponsor-Conducted Epcoritamab Clinical Trials for Clinical Safety

Trial ID **Phase** **First Subject First Visit** **Trial Status**	**Trial Title**	**Trial Design** **Trial Population** **Primary Objective(s)**	**Study Drug(s): Formulation (Route of Administration)** **Dose Regimen** **Duration of Treatment**	**Total Subject Exposure** **Subjects Populations of Interest**	**Number of Subjects Treated (by Treatment Group)**
GCT3013-01 1/2 FSFV: Escalation 26 Jun 2018 Expansion aNHL cohort: 19 Jun 2020 iNHL cohort: 18 Aug 2020 MCL cohort: 09 Feb 2021 Ongoing Data cutoff date: 31 Jan 2022	A Phase 1/2, Open-Label, Dose Escalation Trial of GEN3013 in Patients with Relapsed, Progressive or Refractory B-Cell Lymphoma	First-in-human, open-label, multicenter, multinational, dose escalation (Part 1) and expansion (Part 2) trial Subjects with relapsed, progressive, or refractory B-cell lymphoma Dose escalation (phase 1): Determine MTD and RP2D Expansion (phase 2): Evaluate clinical efficacy as determined by Lugano criteria	Epcoritamab: SC Priming dose /intermediate dose/ full dose administered SC. Treatment cycles of 4 weeks, ie, 28 days. Dose escalation (phase 1): Cycle 1-2: Days 1, 8, 15, and 22 (QW) Cycle 3-6: Days 1 and 15 (Q2W) Cycles 7 to PD, unacceptable toxicity, or end of trial: Day 1 (Q4W) Expansion (phase 2) (RP2D): Cycle 1-3: Days 1, 8, 15, and 22 (QW) Cycle 4-9: Days 1 and 15 (Q2W) Cycles 10 to PD, unacceptable toxicity, or end of trial: Day 1 (Q4W)	Dose escalation (phase 1), n=68 All subjects at 48 mg, n=12 LBCL subjects at 48 mg, n=10 DLBCL subjects at 48 mg, n=9 PMBCL subjects at 48 mg, n=1 FL subjects at 48 mg, n=1 MCL subjects at 48 mg, n=1	Dose escalation (full) 0.0128 mg, n=1 0.04 mg, n=2 0.12 mg, n=4 0.38 mg, n=2 0.76 mg, n=7 1.5 mg, n=5 3 mg, n=6 6 mg, n=9 12 mg, n=7 24 mg, n=10 48 mg, n=12 60 mg, n=3
				Expansion (phase 2) aNHL (LBCL) cohort, n=157 DLBCL, n=139 Other, n=18 HGBCL subjects at 48 mg, n=9 FL3b subjects at 48 mg, n=5 PMBCL subjects at 48 mg, n=4	Expansion 48 mg, n=157

Trial ID **Phase** **First Subject First Visit** **Trial Status**	**Trial Title**	**Trial Design** **Trial Population** **Primary Objective(s)**	**Study Drug(s): Formulation (Route of Administration)** **Dose Regimen** **Duration of Treatment**	**Total Subject Exposure** **Subjects Populations of Interest**	**Number of Subjects Treated (by Treatment Group)**
				iNHL cohort, n=105 (enrollment ongoing) FL, n=92 Other (SLL, MZL), n=13 MCL cohort, n=37 (enrollment ongoing)	48 mg, n=105 48 mg, n=37
GCT3013-04 1/2 FSFV: Escalation 20 Aug 2020 Expansion DLBCL Cohort 06 Jan 2021 FL Cohort 05 Jan 2021 Ongoing Data cutoff date: 31 Jan 2022	Safety and Preliminary Efficacy of Epcoritamab (GEN3013; DuoBody® CD3xCD20) in Japanese Subjects with Relapsed or Refractory (R/R) B-NHL – A Phase 1/2, Open-Label, Dose-Escalation Trial with Expansion Cohorts	Open-label, single-country, interventional trial in Japanese subjects Subjects with R/R B-NHL Dose escalation (Part 1): Determine the MTD and/or the R2PD Expansion (Part 2): Assess the preliminary efficacy of epcoritamab	Epcoritamab: SC Priming dose (0.16 mg)/intermediate dose (0.80 mg)/full dose administered SC. Cycle 1-3: Days 1, 8, 15, 22 (QW) Cycle 4-9: Days 1 and 15 (Q2W) Cycle 10 and beyond: Day 1 (Q4W)	Dose escalation (Part 1), n=9 All subjects at 48 mg, n=6 LBCL subjects at 48 mg, n=5 DLBCL subjects at 48 mg, n=4 HGBCL subjects at 48 mg, n=1 FL subjects at 48 mg, n=1	Dose escalation 24 mg, n=3 48 mg, n=6
				Expansion (Part 2) DLBCL cohort, n=36 FL 1-3a (iNHL) cohort, n=21	Expansion 48 mg, n=36 48 mg, n=21

aNHL = aggressive B-cell non-Hodgkin lymphoma; B-NHL = B-cell non-Hodgkin lymphoma; DLBCL = diffuse large B-cell lymphoma; FIH = first in human; FL = follicular lymphoma; iNHL = indolent B-cell non-Hodgkin lymphoma; LBCL = large B-cell lymphoma; MCL = Mantle cell lymphoma; MTD = maximum tolerated dose; PD = progressive disease; QW = once every week; Q2W = once every 2 weeks; Q4W = once every 4 weeks; R/R = relapsed or refractory; RP2D = recommended phase 2 dose.

Data pooling

In total, data were evaluated from the 374 subjects with various B-cell lymphomas assigned to the 48 mg epcoritamab full dose from the two clinical trials GCT3013-01 and GCT3013-04 (Table 51). The data for subjects treated at the proposed dosing regimen were combined into 2 safety pools and then divided into 5 safety analysis groups as follows:

- Safety Pool 01 [GCT3013-01 (ESC + EXP)]: Combines subject data from the Escalation and Expansion Parts of the global GCT3013-01 trial. The following groups were analysed in Safety Pool 01:
    - LBCL group (N=167) includes subjects with DLBCL (de novo or transformed), PMBCL, HGBCL, and FL grade 3b ***[Primary safety analysis pool]***
    - DLBCL group (N=148) includes subjects with DLBCL (de novo or transformed)

1. Safety Pool 01+04 [GCT3013-01 (ESC + EXP) + GCT3013-04 (ESC + EXP)]: Combines subject data from the Escalation and Expansion Parts of GCT3013-01 with subject data from the Escalation and Expansion Parts of the GCT3013-04 trial conducted in Japan. The following groups were analysed in Safety Pool 01+04:

    2. LBCL group (N=208) includes subjects with DLBCL (de novo or transformed), PMBCL, HGBCL, and FL grade 3b.

    3. DLBCL group (N=188) includes subjects with DLBCL (de novo or transformed)

    4. All B-NHL group (N=374) includes subjects with LBCL, iNHL (128 subjects), and MCL (38 subjects) ***[Supportive safety analysis pool]***

The on-treatment period (treatment-emergent) was defined as the time from day of first dose of trial medication to 60 days (28 days for GCT3013-01 dose escalation) after last dose of trial medication, or initiation of new anti-lymphoma therapy, whichever comes first.

Updated safety analyses

As requested by the CHMP in the D120 LOQ, the applicant presented updated safety analyses based on a more recent data cut-off date (30 June 2022 versus the previous 31 Jan 2022) providing 5 additional months of safety information from the pivotal trial GCT3013-01 and the supportive trial GCT3013-04. The updated safety analyses included no new subjects in the primary safety pool 01 LBCL group (N=167), but 57 additional subjects in the supportive safety pool 01 + 04 All B-NHL group (N=431). The safety evaluation strategy applied to the new data was identical to that used in the initial safety analyses.

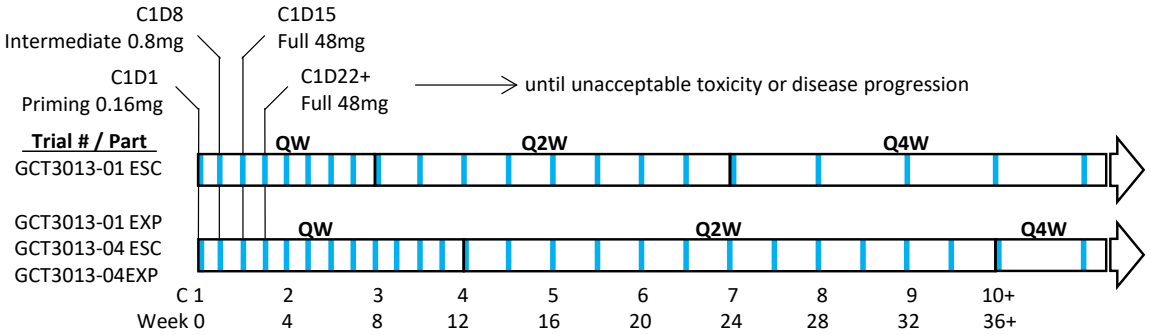
The safety profile of epcoritamab reported in the updated analyses was generally consistent with the reporting in the original submission, and the data presented in this overview are mainly those derived from the initial safety analyses based on the DCO date of 31 Jan 2022. However, findings from the updated analyses are also included where considered relevant.

2.6.8.1. Patient exposure

Exposure

The used posology was epcoritamab administered as a SC injection in 28-day cycles (4 weeks) starting with a QW dosing regimen, followed by administration Q2W and then Q4W (Figure 26). To mitigate the potential for CRS, the first 2 doses of epcoritamab administered on C1D1 (priming dose [0.16 mg]) and C1D8 (intermediate dose [0.8 mg]) were lower than the subsequent full 48-mg dose administered on C1D15, C1D22, and thereafter. Subjects received epcoritamab according to the proposed dosing regimen of 0.16 mg priming dose on C1D1 (except for of 3 subjects in the GCT3013-01 Dose Escalation Part who were in the 0.08 priming cohort), 0.8 mg intermediate dose on C1D8, 48 mg full dose on C1D15, C1D22, and thereafter until disease progression or unacceptable toxicity.

Figure 20: Dosing Regimens in Trials GCT3013-01 and GCT3013-04 – Subjects Enrolled to 48 mg Epcoritamab Treatment



Abbreviations: C = Cycle (28 days); D = Day; ESC = escalation; EXP = expansion; QW = every week (Days 1, 8, 15, and 22); Q2W = every 2 weeks (Days 1 and 15); Q4W = every 4 weeks (Day 1); SC = subcutaneous
Note: Vertical blue lines indicate days of SC epcoritamab administration.

No dose reduction of epcoritamab on an individual subject level was allowed. A re-priming cycle was necessary if dose was delayed at certain time points (eg, >6 weeks between full doses during GCT3013-01 expansion). A re-priming cycle consisted of a weekly schedule of a priming dose, intermediate dose, and 2 full doses.

The recommendations for re-priming were based on PK considerations. Using popPK model estimated individual concentrations, the "safe re-priming window" (*i.e.* time interval since last dose where no re-priming is considered necessary) was defined as the time required for the epcoritamab concentration to drop below priming dose Ctrough in maximum 5% of patients. Consequently, the time interval varies depending on the last dose given (priming dose, intermediate dose, first/second full dose, QW/Q2W/Q4W full dose).

Safety Pool 01: GCT3013-01 (ESC + EXP)

In the Safety Pool 01 LBCL group (N=167), median duration of treatment was 3.7 months (range: 0, 20) and median number of cycles of treatment administered per subject was 5.0 (range 1, 22). The majority of subjects (69.5%) received 3 or more cycles of treatment. A total of 99 (59.3%) subjects initiated C4 treatment, providing a conservative estimation of subjects who received 3 months of treatment. Similarly, 69 (41.3%) subjects initiated C7, approximating 6 months of treatment; 59 (31.5%) subjects initiated C10, approximating 9 months of treatment; 30 (18.0%) subjects initiated C13 treatment, approximating 12 months of treatment. As the data cutoff, 53 (31.7%) subjects were still on treatment (Table 53).

Median RDI was 100.0% during the QW, Q2W, and Q4W dosing schedules. Overall, 62 (37.1%) subjects required a dose delay, including 46 (27.5%) subjects due to an AE and 20 (12.0%) subjects who required a dose delay for another reason, including COVID-19 control measures (Table 52). No subjects required epcoritamab re-priming due to the dose delay.

Safety Pool 01+04: GCT3013-01 (ESC + EXP) + GCT3013-04 (ESC + EXP)

In the Safety Pool 01+04 All B-NHL group (N=374), median duration of treatment was 3.7 months (range: 0, 20) and median number of cycles of treatment administered per subject was 5.0 (range 1, 22). The majority of subjects (71.1%) received 3 or more cycles of treatment. A total of 220 (58.8%) subjects initiated C4 treatment, providing a conservative estimation of subjects who received 3 months of treatment. Similarly, 143 (38.2%) subjects initiated C7, approximating 6 months of treatment; 87 (23.3%) subjects initiated C10, approximating 9 months of treatment; 45 (12.0%) subjects initiated C13 treatment, approximating 12 months of treatment. As the data cutoff, 175 (46.8%) subjects were still on treatment (Table 53).

Median RDI was 100.0% during the QW, Q2W, and Q4W dosing schedules. Overall, 152 (40.6%) subjects required a dose delay, including 124 (33.2%) subjects due to an AE and 42 (11.2%) subjects who required a dose delay for another reason, including COVID-19 control measures (Table 52). Three (0.5%) subjects required epcoritamab re-priming due to a dose delay: 1 LBCL subject (from GCT3013-04) and 2 iNHL subjects. The subject with LBCL required epcoritamab re-priming due to a dose delay of approximately 4 weeks in the receipt of C1D22 dosing due to a TEAE of UTI reactivation. One iNHL subject with SLL had a dose delay due to COVID-19 of approximately 12 weeks following the C5D1 full dose (48 mg) and then had their re-priming dose (0.16 mg) just prior to the data cutoff date. The other iNHL subject with FL had a dose delay of approximately 8 weeks due to serious TEAEs of pneumonia (grade 3) and Bell's palsy (grade 3) and then received 3 additional doses of epcoritamab (0.16 mg priming/0.8 mg intermediate/48 mg full) before the subject withdrew from treatment. The pneumonia was considered related to epcoritamab by the investigator.

Table 39: Epcoritamab Exposure (48 mg Safety Analysis Set – Escalation + Expansion)

	Safety Pool 01		Safety Pool 01+04		
	LBCL (N=167)	DLBCL (N=148)	LBCL (N=208)	DLBCL (N=188)	All B-NHL (N=374)
Number of Cycles Initiated, n (%)					
1	167 (100.0%)	148 (100.0%)	208 (100.0%)	188 (100.0%)	374 (100.0%)
2	143 (85.6%)	126 (85.1%)	180 (86.5%)	163 (86.7%)	322 (86.1%)
3	116 (69.5%)	103 (69.6%)	145 (69.7%)	132 (70.2%)	266 (71.1%)
4	99 (59.3%)	88 (59.5%)	124 (59.6%)	113 (60.1%)	220 (58.8%)
5	88 (52.7%)	79 (53.4%)	110 (52.9%)	101 (53.7%)	189 (50.5%)
6	75 (44.9%)	68 (45.9%)	94 (45.2%)	87 (46.3%)	158 (42.2%)
7	69 (41.3%)	63 (42.6%)	86 (41.3%)	80 (42.6%)	143 (38.2%)
8	62 (37.1%)	59 (39.9%)	78 (37.5%)	75 (39.9%)	121 (32.4%)
9	59 (35.3%)	56 (37.8%)	71 (34.1%)	68 (36.2%)	104 (27.8%)
10	53 (31.7%)	51 (34.5%)	61 (29.3%)	59 (31.4%)	87 (23.3%)
11	44 (26.3%)	42 (28.4%)	52 (25.0%)	50 (26.6%)	73 (19.5%)
12	38 (22.8%)	37 (25.0%)	45 (21.6%)	44 (23.4%)	57 (15.2%)
13 [a]	30 (18.0%)	29 (19.6%)	37 (17.8%)	36 (19.1%)	45 (12.0%)
18	4 (2.4%)	4 (2.7%)	4 (1.9%)	4 (2.1%)	5 (1.3%)
N	167	148	208	188	374
Mean (SD)	6.7 (5.37)	6.9 (5.54)	6.6 (5.22)	6.8 (5.34)	6.1 (4.72)
Median	5.0	5.0	5.0	5.0	5.0
Minimum, Maximum	1, 22	1, 22	1, 22	1, 22	1, 22
Duration of treatment (months)[b]					
N	167	148	208	188	374
Mean (SD)	5.6 (4.87)	5.8 (5.03)	5.6 (4.73)	5.7 (4.85)	5.1 (4.30)
Median	3.7	3.9	4.2	4.2	3.7
Minimum, Maximum	0, 20	0, 20	0, 20	0, 20	0, 20
Number of subjects who received initial intermediate dose, n (%)	**163 (97.6%)**	**144 (97.3%)**	**203 (97.6%)**	**183 (97.3%)**	**362 (96.8%)**
Number of subjects who received initial full dose, n (%)	**156 (93.4%)**	**138 (93.2%)**	**196 (94.2%)**	**177 (94.1%)**	**352 (94.1%)**

	Safety Pool 01		Safety Pool 01+04		
	LBCL (N=167)	**DLBCL (N=148)**	**LBCL (N=208)**	**DLBCL (N=188)**	**All B-NHL (N=374)**
Relative Dose Intensity (%) [c]					
Cycle QW [d]					
N	156	138	161	142	296
Mean (SD)	96.0 (8.40)	96.4 (8.18)	96.1 (8.29)	96.5 (8.08)	94.6 (10.15)
Median	100.0	100.0	100.0	100.0	100.0
Minimum, Maximum	50, 104	50, 104	50, 104	50, 104	37, 104
<50%, n (%)	0	0	0	0	2 (0.7%)
50 - <70%, n (%)	4 (2.6%)	3 (2.2%)	4 (2.5%)	3 (2.1%)	11 (3.7%)
70 - <90%, n (%)	18 (11.5%)	15 (10.9%)	18 (11.2%)	15 (10.6%)	42 (14.2%)
90 - <110%, n (%)	134 (85.9%)	120 (87.0%)	139 (86.3%)	124 (87.3%)	241 (81.4%)
≥110%, n (%)	0	0	0	0	0
Cycle Q2W[e]					
N	101	90	104	93	184
Mean (SD)	98.6 (3.74)	98.5 (3.93)	98.7 (3.69)	98.6 (3.88)	97.9 (6.82)
Median	100.0	100.0	100.0	100.0	100.0
Minimum, Maximum	77, 102	77, 102	77, 102	77, 102	33, 112
<50%, n (%)	0	0	0	0	1 (0.5%)
50 - <70%, n (%)	0	0	0	0	0
70 - <90%, n (%)	3 (3.0%)	3 (3.3%)	3 (2.9%)	3 (3.2%)	10 (5.4%)
90 - <110%, n (%)	98 (97.0%)	87 (96.7%)	101 (97.1%)	90 (96.8%)	172 (93.5%)
≥110%, n (%)	0	0	0	0	1 (0.5%)
Cycle Q4W[f]					
N	53	51	55	53	76
Mean (SD)	99.2 (3.60)	99.1 (3.65)	99.2 (3.53)	99.1 (3.58)	99.2 (3.57)
Median	100.0	100.0	100.0	100.0	100.0
Minimum, Maximum	80, 103	80, 103	80, 103	80, 103	80, 105
<50%, n (%)	0	0	0	0	0
50 - <70%, n (%)	0	0	0	0	0
70 - <90%, n (%)	2 (3.8%)	2 (3.9%)	2 (3.6%)	2 (3.8%)	3 (3.9%)
90 - <110%, n (%)	51 (96.2%)	49 (96.1%)	53 (96.4%)	51 (96.2%)	73 (96.1%)
≥110%, n (%)	0	0	0	0	0
Number of Subjects experiencing dose delay, n (%)	**62 (37.1%)**	**52 (35.1%)**	**77 (37.0%)**	**67 (35.6%)**	**152 (40.6%)**
Reason for dose delay [g]					
Adverse Event	46 (27.5%)	38 (25.7%)	60 (28.8%)	52 (27.7%)	124 (33.2%)
Other [h]	20 (12.0%)	17 (11.5%)	21 (10.1%)	18 (9.6%)	42 (11.2%)
Number of subjects with re-priming [i], n (%)	**0**	**0**	**1 (0.5%)**	**1 (0.5%)**	**3 (0.8%)**

Abbreviations: -01 = GCT3013-01 trial; -04 = GCT3013-04 trial; B-NHL = B-cell non-Hodgkin lymphoma; COVID-19 = coronavirus disease 2019; DLBCL = diffuse large B-cell lymphoma; ESC = escalation; EXP = expansion; FL = follicular lymphoma; FL3B = follicular lymphoma grade 3b; HGBCL = high-grade B-cell lymphoma; iNHL = indolent B-cell non-Hodgkin lymphoma; LBCL = large B-cell lymphoma; MCL = mantle cell lymphoma; PMBCL = primary mediastinal B-cell lymphoma; R/R = relapsed or refractory; SD = standard deviation

Note: Safety Pool 01 includes GCT3013-01. Safety Pool 01+04 includes GCT3013-01 and GCT3013-04. All B-NHL is composed of the LBCL population plus subjects with iNHL (n=128) and MCL (n=38) from the escalation and expansion parts of the trials. Percentages calculated based on N.

[a] Cycles 14 to 22 are provided in the source table.

[b] Duration of treatment calculated as last dose date – first dose date +1

[c] Actual dose intensity is calculated as cumulative dose administered on and after [1s]t full dose divided by duration of dosing period in 28-day cycle. Relative dose intensity is calculated as actual dose intensity divided by planned full dose intensity in the analysis period.

[d] QW = Cycles 1-2 for -01 ESC; Cycles 1-3 for -01 EXP and -04 ESC and EXP

[e] Q2W = Cycles 3-6 for -01 ESC; Cycles 4-9 for -01 EXP and -04 ESC and EXP

[f] Q4W = Cycles 7+ for -01 ESC; Cycles 10+ for -01 EXP and -04 ESC and EXP
[g] Subjects may experience multiple occurrences of dose delay.
[h] Includes subjects who have dose delay due to COVID-19 control measure (e.g., no visits due to quarantine).
[i] Re-priming refers to at least one administration of priming dose after the initial dose of epcoritamab due to extended dose delay.
Data cutoff date:31 Jan 2022
Source: Table 2.1

The median safety follow-up time was 5.6 months (range: <1 to 20 months) in the primary GCT3013-01 ESC+EXP R/R LBCL analysis set and 4.7 months (range: <1 to 20 months) in the supportive GCT3013-01+GCT3013-04 ESC+EXP All B-NHL analysis set.

Subject disposition

Safety Pool 01: GCT3013-01 (ESC + EXP)

In the Safety Pool 01 LBCL group (N=167), 114 (68.3%) subjects discontinued treatment, mostly for the primary reason of disease progression in 87 (52.1%) subjects (Table 53). There were 53 (31.7%) subjects who continued to receive epcoritamab treatment as of the data cutoff. Overall, 12 (7.2%) subjects discontinued study treatment due to a TEAE; these events were assessed by the investigator as unrelated to treatment in 9 of 167 subjects (5.4%) and as treatment-related in 3 of 167 subjects (1.8%) (ICANS, CRS, and CLIPPERS). For 1 (0.6%) subject, the primary reason for discontinuation from study treatment was death, a fatal TEAE of impaired general physical health deterioration in the context of disease progression that was assessed by the investigator as unrelated to treatment. Additional reasons for discontinuation from study treatment included decision to proceed with transplant for 7 (4.2%) subjects, subject withdrawal for 4 (2.4%) subjects, and other for 3 (1.8%) subjects (i.e., physician decision, initiation of new anti-lymphoma treatment, and bridging therapy prior to CAR-T therapy).

Safety Pool 01+04: GCT3013-01 (ESC + EXP) + GCT3013-04 (ESC + EXP)

In the Safety Pool 01+04 All B-NHL group (N=374), 199 (53.2%) subjects discontinued treatment, mostly for the primary reason of disease progression in 147 (39.3%) subjects (Table 53). There were 175 (46.8%) subjects who continued to receive epcoritamab treatment as of the data cutoff.

A higher percentage of subjects remain ongoing in the All B-NHL group (46.8%) compared to the LBCL groups in Safety Pools 01 and 01+04 (31.7% and 33.2%, respectively). This is driven by the GCT3013-01 iNHL expansion cohort (N=105) in the All B-NHL group wherein 67 (63.8%) subjects remained on treatment as of the data cutoff and enrolment is still ongoing. As expected, discontinuation due to disease progression was less in subjects in the iNHL expansion cohort (19.0%) than in the LBCL groups in Safety Pools 01 and 01+04 (52.1% and 52.9%, respectively) due to less aggressive disease.

Overall, 19 (5.1%) subjects discontinued study treatment due to a TEAE; 12 of the subjects were in Safety Pool 01 and are described above. In the other 7 subjects who discontinued study treatment due to a TEAE, the events were assessed by the investigator as unrelated to treatment in 6 of the subjects and as treatment-related in 1 subject with MCL (CRS and multiple organ dysfunction syndrome in the same subject). For 5 (1.3%) subjects in the All B-NHL group (N=374), the primary reason for discontinuation from study treatment was death, either due to fatal TEAEs assessed by the investigator as not related to treatment (general physical health deterioration [described above], pneumonia, lung opacity, or COVID-19 pneumonia) or disease progression. Additional reasons for treatment discontinuation included decision to proceed with transplant for 12 (3.2%) subjects, subject withdrawal for 9 (2.4%) subjects, and other for 7 (1.9%) subjects (i.e., physician decision for 5 subjects, and initiation of new anti-lymphoma treatment and bridging therapy prior to CAR-T therapy in 1 subject each).

Table 40: Disposition (48 mg Safety Analysis Set – Escalation + Expansion)

Number of Subjects, n (%)	Safety Pool 01		Safety Pool 01+04		
	LBCL (N=167)	DLBCL (N=148)	LBCL (N=208)	DLBCL (N=188)	All B-NHL (N=374)
Treated Subjects	**167**	**148**	**208**	**188**	**374**
Ongoing trial treatment	**53 (31.7%)**	**49 (33.1%)**	**69 (33.2%)**	**65 (34.6%)**	**175 (46.8%)**
Discontinued study treatment	**114 (68.3%)**	**99 (66.9%)**	**139 (66.8%)**	**123 (65.4%)**	**199 (53.2%)**
Primary reason for study treatment discontinuation					
Progressive disease [a]	87 (52.1%)	76 (51.4%)	110 (52.9%)	98 (52.1%)	147 (39.3%)
Clinical progression	14 (8.4%)	12 (8.1%)	21 (10.1%)	18 (9.6%)	28 (7.5%)
Disease progression according to response criteria [b]	73 (43.7%)	64 (43.2%)	89 (42.8%)	80 (42.6%)	119 (31.8%)
Adverse event	12 (7.2%)	12 (8.1%)	14 (6.7%)	14 (7.4%)	19 (5.1%)
Death [c]	1 (0.6%)	1 (0.7%)	1 (0.5%)	1 (0.5%)	5 (1.3%)
Withdrawal by subject	4 (2.4%)	3 (2.0%)	4 (1.9%)	3 (1.6%)	9 (2.4%)
Decision to proceed with transplant	7 (4.2%)	5 (3.4%)	7 (3.4%)	5 (2.7%)	12 (3.2%)
Other	3 (1.8%)	2 (1.4%)	3 (1.4%)	2 (1.1%)	7 (1.9%)
Subjects remain on trial	**91 (54.5%)**	**79 (53.4%)**	**117 (56.3%)**	**105 (55.9%)**	**260 (69.5%)**
Discontinued from trial	**76 (45.5%)**	**69 (46.6%)**	**91 (43.8%)**	**83 (44.1%)**	**114 (30.5%)**
Primary reason for trial discontinuation					
Death	65 (38.9%)	59 (39.9%)	80 (38.5%)	73 (38.8%)	99 (26.5%)
Lost to follow-up	1 (0.6%)	1 (0.7%)	1 (0.5%)	1 (0.5%)	1 (0.3%)
Sponsor decision	0	0	0	0	0
Subject withdrew consent from the trial	10 (6.0%)	9 (6.1%)	10 (4.8%)	9 (4.8%)	13 (3.5%)
Other	0	0	0	0	1 (0.3%)

Abbreviations: B-NHL = B-cell non-Hodgkin lymphoma; DLBCL = diffuse large B-cell lymphoma; iNHL = indolent B-cell non-Hodgkin lymphoma; LBCL = large B-cell lymphoma; MCL = mantle cell lymphoma.
Note: Safety Pool 01 includes GCT3013-01. Safety Pool 01+04 includes GCT3013-01 and GCT3013-04. All B-NHL is composed of the LBCL population plus subjects with iNHL (n=128) and MCL (n=38) from the escalation and expansion parts of the trials. Percentages calculated based on N.
[a] Progressive disease includes both clinical progression and documented radiographic disease progression.
[b] The specific category of progression was not collected in the escalation phase of GEN3013-01. Subjects from GCT3013-01 escalation part are included in this sub-category.
[c] None of the deaths were assessed as related to epcoritamab.
Data cutoff date:31 Jan 2022
Source: Table 1.1

2.6.8.2. Adverse events

Overview of adverse events

Safety Pool 01: GCT3013-01 (ESC + EXP)

In the Safety Pool 01 LBCL group (N=167), as of the data cutoff date, 166 (99.4%) subjects experienced at least 1 TEAE (Table 54). Of these, 140 (83.8%) subjects experienced TEAEs considered related to epcoritamab by the investigator. A total of 105 (62.9%) subjects experienced at least 1 grade 3 or higher TEAE, and 47 (28.1%) subjects had grade 3 or higher TEAEs considered related to epcoritamab by the investigator. Serious TEAEs were reported in 97 (58.1%) subjects and were considered related to epcoritamab in 61 (36.5%) subjects.

Fatal TEAEs were reported for 12 (7.2%) subjects; 1 fatal TEAE was assessed as related to epcoritamab by the investigator (a grade 5 ICANS event). TEAEs that led to treatment discontinuation were reported in 13 (7.8%) subjects and to dose delay in 60 (35.9%) subjects. AESIs of CRS were reported for 84 (50.3%) subjects, ICANS in 10 (6.0%) subjects, and CTLS in 2 (1.2%) subjects. Grade 3 or higher AESIs of CRS were reported for 4 (2.4%) subjects, of ICANS for 1 (0.6%) subject, and of CTLS for 2 (1.2%) subjects.

Safety Pool 01+04: GCT3013-01 (ESC + EXP) + GCT3013-04 (ESC + EXP)

TEAE profiles were similar that reported above for Safety Pool 01, except for:

- The incidence of CRS in LBCL subjects (N=208) was higher in Safety Pool 01+04 (57.2%) than in Safety Pool 01 (50.3%) (Table 54), which was driven by the CRS rates reported in GCT3013-04 Escalation Part (83.3%; 5/6 subjects) and Expansion Part (83.3%; 30/36 subjects).
- The incidence of CRS in All B-NHL subjects (N=374) was higher in Safety Pool 01+04 All B-NHL subjects (61.5%) compared to LBCL subjects in Safety Pools 01 and 01+04 (50.3% and 57.2%, respectively) (Table 54), which reflects higher rates of CRS reported in the GCT3013-01 iNHL Expansion Cohort (66.7%; 70/105 subjects) and MCL Expansion Cohort (54.1%; 20/37 subjects); as well as in GCT3013-04 in LBCL (as above) and the GCT3013-04 iNHL (FL) Expansion cohort (90.5%; 19/21 subjects). Grade 3 or 4 CRS in the GCT3013-01 MCL expansion cohort (10.8%; 4/37 subjects) was higher than in Safety Pool 01+04 (4.3%).

Based upon the activity of epcoritamab as a bispecific T-cell engager, CRS, ICANS, and CTLS were considered AESIs in the GCT3013-01 and GCT3013-04 trials. CRS was the most common, reported in approximately 49% to 61% of subjects across groups in Safety Pools 01 and 01+04 (Table 54). The incidences of ICANS and CTLS were approximately 5% to 6% and 1%, respectively. In general, AESIs were primarily grades 1 and 2, resolved, and were manageable with dose delay and/or supportive care. In the section on AESIs, these are discussed in more detail.

Table 41: Overview of Treatment-Emergent Adverse Events (48 mg Safety Analysis Set – Escalation + Expansion)

Number of Subjects, n (%)	Safety Pool 01		Safety Pool 01+04		
	LBCL (N=167)	DLBCL (N=148)	LBCL (N=208)	DLBCL (N=188)	All B-NHL (N=374)
Number of Subjects with ≥1:					
TEAE	166 (99.4%)	147 (99.3%)	207 (99.5%)	187 (99.5%)	368 (98.4%)
Related TEAE	140 (83.8%)	124 (83.8%)	181 (87.0%)	164 (87.2%)	332 (88.8%)
Grade 3 and higher TEAE	105 (62.9%)	94 (63.5%)	141 (67.8%)	129 (68.6%)	248 (66.3%)
Grade 3 and higher related TEAE	47 (28.1%)	42 (28.4%)	79 (38.0%)	73 (38.8%)	145 (38.8%)
TEAE by worst toxicity grade					
1	20 (12.0%)	18 (12.2%)	21 (10.1%)	19 (10.1%)	34 (9.1%)
2	41 (24.6%)	35 (23.6%)	45 (21.6%)	39 (20.7%)	86 (23.0%)
3	62 (37.1%)	56 (37.8%)	79 (38.0%)	73 (38.8%)	144 (38.5%)
4	31 (18.6%)	27 (18.2%)	50 (24.0%)	45 (23.9%)	85 (22.7%)
5	12 (7.2%)	11 (7.4%)	12 (5.8%)	11 (5.9%)	19 (5.1%)
Serious TEAE	97 (58.1%)	87 (58.8%)	113 (54.3%)	102 (54.3%)	218 (58.3%)
Serious related TEAE	61 (36.5%)	54 (36.5%)	74 (35.6%)	66 (35.1%)	151 (40.4%)
TEAE leading to treatment discontinuation	13 (7.8%)	12 (8.1%)	15 (7.2%)	14 (7.4%)	24 (6.4%)
TEAE leading to dose delay	60 (35.9%)	51 (34.5%)	76 (36.5%)	67 (35.6%)	151 (40.4%)
Fatal TEAE[a]	12 (7.2%)	11 (7.4%)	12 (5.8%)	11 (5.9%)	19 (5.1%)
Fatal related TEAE	1 (0.6%)	1 (0.7%)	1 (0.5%)	1 (0.5%)	1 (0.3%)

Number of Subjects, n (%)	Safety Pool 01		Safety Pool 01+04		
	LBCL (N=167)	DLBCL (N=148)	LBCL (N=208)	DLBCL (N=188)	All B-NHL (N=374)
AESI					
CRS					
All grade	84 (50.3%)	73 (49.3%)	119 (57.2%)	107 (56.9%)	230 (61.5%)
Grade 3 and higher	4 (2.4%)	4 (2.7%)	8 (3.8%)	8 (4.3%)	16 (4.3%)
ICANS					
All grade	10 (6.0%)	9 (6.1%)	11 (5.3%)	10 (5.3%)	23 (6.1%)
Grade 3 and higher	1 (0.6%)	1 (0.7%)	1 (0.5%)	1 (0.5%)	1 (0.3%)
CTLS					
All grade	2 (1.2%)	2 (1.4%)	3 (1.4%)	2 (1.1%)	5 (1.3%)
Grade 3 and higher	2 (1.2%)	2 (1.4%)	3 (1.4%)	2 (1.1%)	3 (0.8%)

Abbreviations: AESI = adverse event of special interest; B-NHL = B-cell non-Hodgkin lymphoma; CRS = cytokine release syndrome; CTCAE = Common Terminology Criteria for Adverse Events; CTLS = clinical tumor lysis syndrome; DLBCL = diffuse large B-cell lymphoma; ICANS = immune effector cell-associated neurotoxicity syndrome; iNHL = indolent B-cell non-Hodgkin lymphoma; LBCL = large B-cell lymphoma; MCL = mantle cell lymphoma; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.
[a] 4 of the subjects in All B-NHL reported in this row (4, 3, 4, and 3 of the subjects in each column, respectively) are also reported by investigator with primary cause of death as disease progression.
Note: Safety Pool 01 includes GCT3013-01. Safety Pool 01+04 includes GCT3013-01 and GCT3013-04. All B-NHL is composed of the LBCL population plus subjects with iNHL (n=128) and MCL (n=38) from the escalation and expansion parts of the trials. Percentages calculated based on N.
Note: Adverse events are classified using MedDRA v24.1 and CTCAE v5.0, and are counted only once per category. ICANS is graded according to (Lee et al 2019), CRS as per (Lee et al 2019), and CTLS according to Cairo-Bishop (Coiffier et al 2008).
Data cutoff date:31 Jan 2022
Source: Table 3.1

In the Safety Pool GCT3013-01 ESC+EXP R/R LBCL group (primary safety analysis pool), the majority of all TEAEs, Grade ≥3 TEAEs, and serious AEs were reported as recovered/resolved (78.3%, 64.4%, and 80.1%, respectively). The corresponding percentages of treatment-related events with an outcome of recovered/resolved were higher (all, 88.6%; Grade ≥3, 73.7%; and serious, 93.3%). Events (any or treatment-related) with other outcomes were most generally reported as not recovered/not resolved, and few had a fatal outcome. Overall, 0.2% of TEAEs were reported as recovered/resolved with sequelae; all of these were nonserious.

Regarding AESIs, an outcome of recovered/resolved was reported for 98.4% of CRS events, 90.0% of ICANS events, and 33.3% of CTLS events. The few remaining AESI occurrences were either not recovered/not resolved (2 events each for CRS and CTLS) or fatal (1 event of ICANS).

In the Safety Pool GCT3013-01+ GCT3013-04 ESC+EXP All B-NHL group (supportive safety analysis pool), the outcome distribution pattern for all TEAEs, Grade ≥3 TEAEs, and serious AEs (any or treatment-related) was similar to that of the primary safety analysis pool.

TEAEs over time

TEAEs were analysed over time following initial epcoritamab administration. Interpretation of these data require consideration of the length of time and dosing schedules during each time period chosen for analysis. Dosing schedules were changed after the Escalation Part of trial GCT3013-01 as shown in Figure 26 resulting in differences in doses of epcoritamab with the GCT3013-01 Expansion Part and the GCT3013-04 Escalation and Expansion Parts.

Safety Pool 01: GCT3013-01 (ESC + EXP)

In the Safety Pool 01 LBCL group (N=167), the incidence of TEAEs and TEAEs considered related to epcoritamab by the investigator, both overall and grade 3 and higher, as well as serious TEAEs and

serious TEAEs considered related to epcoritamab by the investigator was greater during the initial treatment period up to week 8 compared with any of the subsequent treatment periods. Most AESIs occurred early in treatment. Of the 84 total subjects with CRS, only 3 were reported to have CRS after the Week ≤8 period; similarly, only 1 out of the 10 subjects with ICANS, and 0 out of the 2 subjects with CTLS, had these events after Week 8. All grade 3 or higher AESIs were reported during the Week ≤8 period.

Safety Pool 01+04: GCT3013-01 (ESC + EXP) + GCT3013-04 (ESC + EXP)

In the Safety Pool 01+04 All B-NHL group (N=374), the incidence of TEAEs and TEAEs considered related to epcoritamab by the investigator, both overall and grade 3 and higher, as well as serious TEAEs and serious TEAEs considered related to epcoritamab by the investigator was greater during the initial treatment period up to week 8 compared with any of the subsequent treatment periods. Most AESIs occurred early in treatment. Of the 230 subjects with CRS, only 9 were reported to have CRS after the Week ≤8 period; similarly, only 2 out of the 23 subjects with ICANS, and 0 out of 5 with CTLS, had these events after Week 8. All grade 3 or higher AESIs were reported during the Week ≤8 period.

Safety update (DCO 30 June 2022): Consistent with the initial results, the overall incidence of TEAEs, both overall and grade 3 or 4, as well as serious TEAEs and serious TEAEs considered related to epcoritamab by the investigator were greater during the initial treatment period up to Week 8 compared with any of the subsequent treatment periods. Most AESIs occurred during the Week ≤8 period.

Common adverse events

Safety Pool 01: GCT3013-01 (ESC + EXP)

In the Safety Pool 01 LBCL group (N=167):

TEAEs reported in ≥10% of subjects included CRS (50.3%); fatigue (24.6%); pyrexia (22.8%); injection site reaction and neutropenia (22.2% each); nausea (20.4%), diarrhea (19.8%); anemia (18.0%); abdominal pain (13.8%); thrombocytopenia (13.2%); headache (12.6%); constipation and vomiting (12.0% each); decreased appetite and edema peripheral (11.4% each); and back pain and insomnia (10.8% each) (Table 55).

Safety Pool 01+04: GCT3013-01 (ESC + EXP) + GCT3013-04 (ESC + EXP)

In the Safety Pool 01+04 All B-NHL group (N=374):

TEAEs reported in ≥10% of subjects included CRS (61.5%), injection site reaction (31.0%), fatigue (22.7%), pyrexia (21.9%), diarrhea (18.4%), neutropenia (18.2%), nausea (17.6%), anemia (15.0%), constipation (13.1%), headache (12.6%), decreased appetite (11.0%), neutrophil count decreased (10.7%), and insomnia (10.4%) (Table 55).

Table 42: Treatment-Emergent Adverse Events in at Least 10% of Subjects in Any Group by SOC and PT (48 mg Safety Analysis Set – Escalation + Expansion)

System Organ Class Preferred Term, n (%)	Safety Pool 01				Safety Pool 01+04					
	LBCL (N=167)		DLBCL (N=148)		LBCL (N=208)		DLBCL (N=188)		All B-NHL (N=374)	
	All	Related	All	Related	All	Related	All	Related	All	Related
Subjects with ≥1 TEAE	166 (99.4%)	140 (83.8%)	147 (99.3%)	124 (83.8%)	207 (99.5%)	181 (87.0%)	187 (99.5%)	164 (87.2%)	368 (98.4%)	332 (88.8%)
General disorders	109	77	99	69	143	107	133	99	262	201

System Organ Class Preferred Term, n (%)	Safety Pool 01				Safety Pool 01+04					
	LBCL (N=167)		DLBCL (N=148)		LBCL (N=208)		DLBCL (N=188)		All B-NHL (N=374)	
	All	Related	All	Related	All	Related	All	Related	All	Related
and administration site conditions	**(65.3%)**	**(46.1%)**	**(66.9%)**	**(46.6%)**	**(68.8%)**	**(51.4%)**	**(70.7%)**	**(52.7%)**	**(70.1%)**	**(53.7%)**
Injection site reaction	37 (22.2%)	37 (22.2%)	35 (23.6%)	35 (23.6%)	59 (28.4%)	59 (28.4%)	57 (30.3%)	57 (30.3%)	116 (31.0%)	115 (30.7%)
Pyrexia	38 (22.8%)	19 (11.4%)	33 (22.3%)	15 (10.1%)	42 (20.2%)	22 (10.6%)	37 (19.7%)	18 (9.6%)	82 (21.9%)	40 (10.7%)
Fatigue	41 (24.6%)	25 (15.0%)	38 (25.7%)	23 (15.5%)	41 (19.7%)	25 (12.0%)	38 (20.2%)	23 (12.2%)	85 (22.7%)	50 (13.4%)
Injection site erythema	14 (8.4%)	14 (8.4%)	14 (9.5%)	14 (9.5%)	20 (9.6%)	20 (9.6%)	20 (10.6%)	20 (10.6%)	34 (9.1%)	33 (8.8%)
Oedema peripheral	19 (11.4%)	3 (1.8%)	18 (12.2%)	3 (2.0%)	19 (9.1%)	3 (1.4%)	18 (9.6%)	3 (1.6%)	33 (8.8%)	4 (1.1%)
Gastrointestinal disorders	**105 (62.9%)**	**28 (16.8%)**	**95 (64.2%)**	**26 (17.6%)**	**130 (62.5%)**	**42 (20.2%)**	**119 (63.3%)**	**39 (20.7%)**	**215 (57.5%)**	**72 (19.3%)**
Nausea	34 (20.4%)	13 (7.8%)	32 (21.6%)	12 (8.1%)	43 (20.7%)	16 (7.7%)	40 (21.3%)	14 (7.4%)	66 (17.6%)	25 (6.7%)
Diarrhoea	33 (19.8%)	8 (4.8%)	30 (20.3%)	8 (5.4%)	38 (18.3%)	12 (5.8%)	35 (18.6%)	12 (6.4%)	69 (18.4%)	22 (5.9%)
Constipation	20 (12.0%)	2 (1.2%)	18 (12.2%)	2 (1.4%)	26 (12.5%)	4 (1.9%)	24 (12.8%)	4 (2.1%)	49 (13.1%)	7 (1.9%)
Abdominal pain	23 (13.8%)	5 (3.0%)	21 (14.2%)	4 (2.7%)	25 (12.0%)	5 (2.4%)	23 (12.2%)	4 (2.1%)	35 (9.4%)	7 (1.9%)
Vomiting	20 (12.0%)	3 (1.8%)	19 (12.8%)	3 (2.0%)	24 (11.5%)	6 (2.9%)	23 (12.2%)	6 (3.2%)	34 (9.1%)	9 (2.4%)
Immune system disorders	**87 (52.1%)**	**84 (50.3%)**	**76 (51.4%)**	**73 (49.3%)**	**122 (58.7%)**	**119 (57.2%)**	**110 (58.5%)**	**107 (56.9%)**	**234 (62.6%)**	**231 (61.8%)**
Cytokine release syndrome	84 (50.3%)	84 (50.3%)	73 (49.3%)	73 (49.3%)	119 (57.2%)	119 (57.2%)	107 (56.9%)	107 (56.9%)	230 (61.5%)	230 (61.5%)
Metabolism and nutrition disorders	**63 (37.7%)**	**15 (9.0%)**	**57 (38.5%)**	**13 (8.8%)**	**86 (41.3%)**	**31 (14.9%)**	**79 (42.0%)**	**28 (14.9%)**	**145 (38.8%)**	**50 (13.4%)**
Decreased appetite	19 (11.4%)	3 (1.8%)	18 (12.2%)	3 (2.0%)	28 (13.5%)	11 (5.3%)	27 (14.4%)	11 (5.9%)	41 (11.0%)	19 (5.1%)
Hypokalaemia	14 (8.4%)	1 (0.6%)	14 (9.5%)	1 (0.7%)	26 (12.5%)	7 (3.4%)	26 (13.8%)	7 (3.7%)	37 (9.9%)	8 (2.1%)
Investigations	**54 (32.3%)**	**22 (13.2%)**	**49 (33.1%)**	**20 (13.5%)**	**84 (40.4%)**	**48 (23.1%)**	**78 (41.5%)**	**45 (23.9%)**	**146 (39.0%)**	**91 (24.3%)**
Neutrophil count decreased	10 (6.0%)	6 (3.6%)	7 (4.7%)	4 (2.7%)	25 (12.0%)	19 (9.1%)	22 (11.7%)	17 (9.0%)	40 (10.7%)	32 (8.6%)
Blood and lymphatic system disorders	**68 (40.7%)**	**45 (26.9%)**	**61 (41.2%)**	**40 (27.0%)**	**80 (38.5%)**	**55 (26.4%)**	**73 (38.8%)**	**50 (26.6%)**	**136 (36.4%)**	**93 (24.9%)**
Neutropenia	37 (22.2%)	30 (18.0%)	35 (23.6%)	28 (18.9%)	38 (18.3%)	31 (14.9%)	36 (19.1%)	29 (15.4%)	68 (18.2%)	54 (14.4%)
Anaemia	30 (18.0%)	10 (6.0%)	28 (18.9%)	10 (6.8%)	37 (17.8%)	15 (7.2%)	35 (18.6%)	15 (8.0%)	56 (15.0%)	23 (6.1%)
Thrombocytopenia	22 (13.2%)	8 (4.8%)	21 (14.2%)	8 (5.4%)	23 (11.1%)	9 (4.3%)	22 (11.7%)	9 (4.8%)	35 (9.4%)	16 (4.3%)
Musculoskeletal and connective tissue disorders	**62 (37.1%)**	**14 (8.4%)**	**56 (37.8%)**	**11 (7.4%)**	**70 (33.7%)**	**15 (7.2%)**	**64 (34.0%)**	**12 (6.4%)**	**117 (31.3%)**	**30 (8.0%)**
Back pain	18 (10.8%)	1 (0.6%)	15 (10.1%)	0	21 (10.1%)	1 (0.5%)	18 (9.6%)	0	32 (8.6%)	4 (1.1%)

System Organ Class Preferred Term, n (%)	Safety Pool 01				Safety Pool 01+04					
	LBCL (N=167)		DLBCL (N=148)		LBCL (N=208)		DLBCL (N=188)		All B-NHL (N=374)	
	All	Related	All	Related	All	Related	All	Related	All	Related
Nervous system disorders	**57 (34.1%)**	**23 (13.8%)**	**49 (33.1%)**	**19 (12.8%)**	**67 (32.2%)**	**26 (12.5%)**	**58 (30.9%)**	**22 (11.7%)**	**128 (34.2%)**	**57 (15.2%)**
Headache	21 (12.6%)	9 (5.4%)	17 (11.5%)	6 (4.1%)	24 (11.5%)	9 (4.3%)	20 (10.6%)	6 (3.2%)	47 (12.6%)	18 (4.8%)
Psychiatric disorders	**28 (16.8%)**	**3 (1.8%)**	**26 (17.6%)**	**3 (2.0%)**	**35 (16.8%)**	**3 (1.4%)**	**32 (17.0%)**	**3 (1.6%)**	**69 (18.4%)**	**9 (2.4%)**
Insomnia	18 (10.8%)	2 (1.2%)	16 (10.8%)	2 (1.4%)	22 (10.6%)	2 (1.0%)	19 (10.1%)	2 (1.1%)	39 (10.4%)	2 (0.5%)

Abbreviations: B-NHL = B-cell non-Hodgkin lymphoma; DLBCL = diffuse large B-cell lymphoma; iNHL = indolent B-cell non-Hodgkin lymphoma; LBCL = large B-cell lymphoma; MCL = mantle cell lymphoma; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SOC = system organ class; TEAE = treatment-emergent adverse event.
Note: Safety Pool 01 includes GCT3013-01. Safety Pool 01+04 includes GCT3013-01 and GCT3013-04. All B-NHL is composed of the LBCL population plus subjects with iNHL (n=128) and MCL (n=38) from the escalation and expansion parts of the trials. Percentages calculated based on N. Sorted by descending frequency in the Safety Pool 01+04 LBCL All column.
Note: Adverse events are classified using MedDRA v24.1 and are counted only once per system organ class and only once per preferred term.
Data cutoff date:31 Jan 2022
Source: Table 3.3

Regarding the incidences of TEAEs over time:

Safety Pool 01: GCT3013-01 (ESC + EXP)

In the Safety Pool 01 LBCL group (N=167), the highest incidences of TEAEs over time were during the first period (Week ≤8). This was true for all SOCs except for Infections and infestations, which had similar incidences during the Week ≤8 period (26.9% of 167 subjects), Week 12 to ≤36 period (28.8% of 104 subjects), and Week 36+ period (28.3% of 53 subjects).

Safety Pool 01+04: GCT3013-01 (ESC + EXP) + GCT3013-04 (ESC + EXP)

In the Safety Pool 01+04 All B-NHL group (N=374), the highest incidences of TEAEs over time were during the first period (Week ≤8). This was true for all SOCs except for Infections and infestations, which had similar incidences during the Week ≤8 period (27.8% of 374 subjects), the Week 12 to ≤36 period (29.4% of 235 subjects), and the Week 36+ period (30.4% of 92 subjects).

The updated safety analyses (DCO 30 June 2022) confirmed that the highest incidences of TEAEs over time were during the first period (Week ≤8), except for the incidence for the Infections and infestations SOC. This is further discussed in the section on Infections later in this overview.

Grade 3 or higher treatment-emergent adverse events

Grade 3 or higher TEAEs by SOC and PT in Safety Pools 01 and 01+04 are provided in Table 56, summarized by frequency of grade 3 or 4 TEAEs (≥5% of subjects) and all fatal TEAEs (TEAEs that resulted in death). Cytopenias were the only grade ≥3 TEAEs reported in ≥5% of subjects. Cytopenias (e.g., neutropenia, anemia, thrombocytopenia) were managed through dose delay and/or G-CSF for neutropenia. No TEAEs of any cytopenia led to treatment discontinuation.

Safety Pool 01: GCT3013-01 (ESC + EXP)

In the Safety Pool 01 LBCL group (N=167), out of 166 (99.4%) subjects with ≥1 TEAE, the range of worst severity grades were as follows (Table 54): Grade 1 = 20 (12.0%) subjects, Grade 2 = 41

(24.6%) subjects, Grade 3 = 62 (37.1%) subjects, Grade 4 = 31 (18.6%) subjects, and Grade 5 = 12 (7.2%) subjects.

In Safety Pool 01 LBCL subjects, grade 3 or 4 TEAEs reported in ≥5% of subjects included neutropenia in 26 (15.6%) subjects, anemia in 17 (10.2%) subjects, and neutrophil count deceased and thrombocytopenia in 10 (6.0%) subjects (Table 56).

Safety Pool 01+04: GCT3013-01 (ESC + EXP) + GCT3013-04 (ESC + EXP)

In the Safety Pool 01+04 All B-NHL group (N=374), out of 368 (98.4%) subjects with ≥1 TEAE, the range of worst severity grades were as follows (Table 54): Grade 1 = 34 (9.1%) subjects, Grade 2 = 86 (23.0%) subjects, Grade 3 = 144 (38.5%) subjects, Grade 4 = 85 (22.7%) subjects, Grade 5 = 19 (5.1%) subjects.

In Safety Pool 01+04 All B-NHL subjects, grade 3 or 4 TEAEs reported in ≥5% of subjects included neutropenia in 52 (13.9%) subjects, neutrophil count deceased in 37 (9.9%) subjects, anemia in 32 (8.6%) subjects, lymphocyte count decreased in 24 (6.4%) subjects, and thrombocytopenia in 20 (5.3%) subjects (Table 56).

Table 43: Grade 3 or 4 TEAEs in ≥5% of Subjects in Any Group and Fatal TEAEs by SOC and PT (48 mg Safety Analysis Set – Escalation + Expansion)

System Organ Class / Preferred Term, n (%)	Safety Pool 01				Safety Pool 01+04					
	LBCL (N=167)		DLBCL (N=148)		LBCL (N=208)		DLBCL (N=188)		All B-NHL (N=374)	
	Grade 3-4	Fatal	Grade 3-4	Fatal	Grade 3-4	Fatal	Grade 3-4	Fatal	Grade 3-4	Fatal
Subjects with ≥1 TEAE	**100 (59.9%)**	**12 (7.2%)**	**89 (60.1%)**	**11 (7.4%)**	**136 (65.4%)**	**12 (5.8%)**	**124 (66.0%)**	**11 (5.9%)**	**239 (63.9%)**	**19 (5.1%)**
Blood and lymphatic system disorders	**46 (27.5%)**	**0**	**42 (28.4%)**	**0**	**53 (25.5%)**	**0**	**49 (26.1%)**	**0**	**97 (25.9%)**	**0**
Neutropenia	26 (15.6%)	0	25 (16.9%)	0	27 (13.0%)	0	26 (13.8%)	0	52 (13.9%)	0
Anaemia	17 (10.2%)	0	17 (11.5%)	0	22 (10.6%)	0	22 (11.7%)	0	32 (8.6%)	0
Thrombocytopenia	10 (6.0%)	0	9 (6.1%)	0	11 (5.3%)	0	10 (5.3%)	0	20 (5.3%)	0
Infections and infestations	**24 (14.4%)**	**4 (2.4%)**	**21 (14.2%)**	**4 (2.7%)**	**31 (14.9%)**	**4 (1.9%)**	**28 (14.9%)**	**4 (2.1%)**	**62 (16.6%)**	**9 (2.4%)**
COVID-19	4 (2.4%)	2 (1.2%)	4 (2.7%)	2 (1.4%)	4 (1.9%)	2 (1.0%)	4 (2.1%)	2 (1.1%)	7 (1.9%)	2 (0.5%)
COVID-19 pneumonia	2 (1.2%)	1 (0.6%)	1 (0.7%)	1 (0.7%)	2 (1.0%)	1 (0.5%)	1 (0.5%)	1 (0.5%)	4 (1.1%)	2 (0.5%)
Progressive multifocal leukoencephalopathy	0	1 (0.6%)	0	1 (0.7%)	0	1 (0.5%)	0	1 (0.5%)	0	1 (0.3%)
Necrotising fasciitis	0	0	0	0	0	0	0	0	0	1 (0.3%)
Pneumonia	3 (1.8%)	0	3 (2.0%)	0	4 (1.9%)	0	4 (2.1%)	0	7 (1.9%)	1 (0.3%)
Pneumonia aspiration	0	0	0	0	0	0	0	0	0	1 (0.3%)
Septic shock	2 (1.2%)	0	2 (1.4%)	0	2 (1.0%)	0	2 (1.1%)	0	3 (0.8%)	1 (0.3%)
Investigations	**22 (13.2%)**	**0**	**19 (12.8%)**	**0**	**47 (22.6%)**	**0**	**44 (23.4%)**	**0**	**83 (22.2%)**	**0**

System Organ Class Preferred Term, n (%)	Safety Pool 01				Safety Pool 01+04					
	LBCL (N=167)		DLBCL (N=148)		LBCL (N=208)		DLBCL (N=188)		All B-NHL (N=374)	
	Grade 3-4	Fatal	Grade 3-4	Fatal	Grade 3-4	Fatal	Grade 3-4	Fatal	Grade 3-4	Fatal
Neutrophil count decreased	10 (6.0%)	0	7 (4.7%)	0	25 (12.0%)	0	22 (11.7%)	0	37 (9.9%)	0
Lymphocyte count decreased	4 (2.4%)	0	4 (2.7%)	0	15 (7.2%)	0	15 (8.0%)	0	24 (6.4%)	0
General disorders and administration site conditions	**9 (5.4%)**	**2 (1.2%)**	**8 (5.4%)**	**2 (1.4%)**	**10 (4.8%)**	**2 (1.0%)**	**9 (4.8%)**	**2 (1.1%)**	**19 (5.1%)**	**2 (0.5%)**
General physical health deterioration	0	2 (1.2%)	0	2 (1.4%)	0	2 (1.0%)	0	2 (1.1%)	0	2 (0.5%)
Nervous system disorders	**6 (3.6%)**	**2 (1.2%)**	**6 (4.1%)**	**2 (1.4%)**	**7 (3.4%)**	**2 (1.0%)**	**6 (3.2%)**	**2 (1.1%)**	**12 (3.2%)**	**2 (0.5%)**
Cerebral haemorrhage	0	0	0	0	0	0	0	0	0	0
Immune effector cell-associated neurotoxicity syndrome	0	1 (0.6%)	0	1 (0.7%)	0	1 (0.5%)	0	1 (0.5%)	0	1 (0.3%)
Loss of consciousness	0	1 (0.6%)	0	1 (0.7%)	0	1 (0.5%)	0	1 (0.5%)	0	1 (0.3%)
Cardiac disorders	**5 (3.0%)**	**1 (0.6%)**	**4 (2.7%)**	**1 (0.7%)**	**5 (2.4%)**	**1 (0.5%)**	**4 (2.1%)**	**1 (0.5%)**	**8 (2.1%)**	**1 (0.3%)**
Myocardial infarction	0	1 (0.6%)	0	1 (0.7%)	0	1 (0.5%)	0	1 (0.5%)	0	1 (0.3%)
Hepatobiliary disorders	**2 (1.2%)**	**1 (0.6%)**	**2 (1.4%)**	**1 (0.7%)**	**2 (1.0%)**	**1 (0.5%)**	**2 (1.1%)**	**1 (0.5%)**	**3 (0.8%)**	**1 (0.3%)**
Hepatotoxicity	0	1 (0.6%)	0	1 (0.7%)	0	1 (0.5%)	0	1 (0.5%)	0	1 (0.3%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**5 (3.0%)**	**1 (0.6%)**	**5 (3.4%)**	**0**	**7 (3.4%)**	**1 (0.5%)**	**7 (3.7%)**	**0**	**9 (2.4%)**	**2 (0.5%)**
Malignant neoplasm progression	0	1 (0.6%)	0	0	0	1 (0.5%)	0	0	0	1 (0.3%)
Lymphoma transformation	0	0	0	0	0	0	0	0	0	1 (0.3%)
Respiratory, thoracic and mediastinal disorders	**11 (6.6%)**	**1 (0.6%)**	**10 (6.8%)**	**1 (0.7%)**	**11 (5.3%)**	**1 (0.5%)**	**10 (5.3%)**	**1 (0.5%)**	**18 (4.8%)**	**2 (0.5%)**
Pulmonary embolism	0	1 (0.6%)	0	1 (0.7%)	0	1 (0.5%)	0	1 (0.5%)	3 (0.8%)	1 (0.3%)
Lung opacity	0	0	0	0	0	0	0	0	0	1 (0.3%)

Abbreviations: B-NHL = B-cell non-Hodgkin lymphoma; COVID-19 = coronavirus disease 2019; CTCAE = Common Terminology Criteria for Adverse Events; DLBCL = diffuse large B-cell lymphoma; iNHL = indolent B-cell non-Hodgkin lymphoma; LBCL = large B-cell lymphoma; MCL = mantle cell lymphoma; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SOC = system organ class; TEAE = treatment-emergent adverse event.

Note: Safety Pool 01 includes GCT3013-01. Safety Pool 01+04 includes GCT3013-01 and GCT3013-04. All B-NHL is composed of the LBCL population plus subjects with iNHL (n=128) and MCL (n=38) from the escalation and expansion parts of the trials. Percentages calculated based on N. Sorted by descending frequency in the Safety Pool 01+04 LBCL grade 3-4 column.

Note: Adverse events are classified using MedDRA v24.1 and are counted only once per system organ class and only once per preferred term.

Note : Events are graded according to CTCAE v5.0.

Data cutoff date:31 Jan 2022

Source: Table 3.11, Table 3.12

Treatment-related TEAEs based on investigator assessment

The most frequently reported TEAEs in Safety Pools 01 and 01+04 assessed by the investigator as treatment-related are summarized in Table 55. In general, most TEAEs considered related to epcoritamab by the investigator were low-grade (grade 1 or 2). There was 1 treatment-related fatal AE of ICANS.

Safety Pool 01: GCT3013-01 (ESC + EXP)

In the Safety Pool 01 LBCL group (N=167), out of 140 (83.8%) subjects who experienced ≥1 TEAE considered treatment-related by the investigator, 47 (28.1%) subjects had ≥1 grade 3 or higher treatment-related TEAE:

Treatment-related TEAEs reported in ≥10% of subjects included CRS in 84 (50.3%) subjects, injection site reaction in 37 (22.2%) subjects, neutropenia in 30 (18.0%) subjects, fatigue in 25 (15.0%) subjects, and pyrexia in 19 (11.4%) subjects.

- Grade 3 or higher treatment-related adverse events reported in ≥2% of subjects included neutropenia in 19 (11.4%) subjects; neutrophil count deceased in 6 (3.6%) subjects; and anemia and CRS in 4 (2.4%) subjects each (Table 57).

Safety Pool 01+04: GCT3013-01 (ESC + EXP) + GCT3013-04 (ESC + EXP)

In the Safety Pool 01+04 All B-NHL group (N=374), out of 332 (88.8%) subjects who experienced ≥1 TEAE considered treatment-related by the investigator, 145 (38.8%) subjects had ≥1 grade 3 or higher treatment-related TEAEs:

- Treatment-related TEAEs reported in ≥10% of subjects included CRS in 230 (61.5%) subjects, injection site reaction in 115 (30.7%) subjects, neutropenia in 54 (14.4%) subjects, fatigue in 50 (13.4%) subjects, and pyrexia in 40 (10.7%) subjects.
- Grade 3 or higher treatment-related TEAEs reported in ≥2% of subjects included neutropenia in 39 (10.4%) subjects; neutrophil count decreased in 29 (7.8%) subjects; lymphocyte count decreased in 17 (4.5%) subjects; CRS in 16 (4.3%) subjects; anemia, thrombocytopenia, and platelet count decreased in 10 (2.7%) subjects each; and lymphopenia in 8 (2.1%) subjects (Table 57).

Table 44: Treatment-Related Grade 3 or 4 TEAEs in at Least 2% of Subjects in Any Group and Fatal TEAEs by SOC and PT - Investigator Assessment (48 mg Safety Analysis Set – Escalation + Expansion)

System Organ Class Preferred Term, n (%)	Safety Pool 01				Safety Pool 01+04					
	LBCL (N=167)		DLBCL (N=148)		LBCL (N=208)		DLBCL (N=188)		All B-NHL (N=374)	
	Grade 3-4	Fatal	Grade 3-4	Fatal	Grade 3-4	Fatal	Grade 3-4	Fatal	Grade 3-4	Fatal

Subjects with ≥1	**47 (28.1%)**	**1 (0.6%)**	**42 (28.4%)**	**1 (0.7%)**	**79 (38.0%)**	**1 (0.5%)**	**73 (38.8%)**	**1 (0.5%)**	**145 (38.8%)**	**1 (0.3%)**
Blood and lymphatic system disorders	**27 (16.2%)**	**0**	**24 (16.2%)**	**0**	**32 (15.4%)**	**0**	**29 (15.4%)**	**0**	**61 (16.3%)**	**0**
Neutropenia	19 (11.4%)	0	18 (12.2%)	0	20 (9.6%)	0	19 (10.1%)	0	39 (10.4%)	0
Anaemia	4 (2.4%)	0	4 (2.7%)	0	7 (3.4%)	0	7 (3.7%)	0	10 (2.7%)	0
Thrombocytopenia	3 (1.8%)	0	3 (2.0%)	0	4 (1.9%)	0	4 (2.1%)	0	10 (2.7%)	0
Lymphopenia	3 (1.8%)	0	2 (1.4%)	0	3 (1.4%)	0	2 (1.1%)	0	8 (2.1%)	0
Investigations	**8 (4.8%)**	**0**	**6 (4.1%)**	**0**	**30 (14.4%)**	**0**	**28 (14.9%)**	**0**	**59 (15.8%)**	**0**
Neutrophil count decreased	6 (3.6%)	0	4 (2.7%)	0	18 (8.7%)	0	16 (8.5%)	0	29 (7.8%)	0
Lymphocyte count decreased	1 (0.6%)	0	1 (0.7%)	0	10 (4.8%)	0	10 (5.3%)	0	17 (4.5%)	0
White blood cell count decreased	0	0	0	0	6 (2.9%)	0	6 (3.2%)	0	7 (1.9%)	0
Platelet count decreased	1 (0.6%)	0	1 (0.7%)	0	6 (2.9%)	0	6 (3.2%)	0	10 (2.7%)	0
Immune system disorders	**4 (2.4%)**	**0**	**4 (2.7%)**	**0**	**8 (3.8%)**	**0**	**8 (4.3%)**	**0**	**17 (4.5%)**	**0**
Cytokine release syndrome	4 (2.4%)	0	4 (2.7%)	0	8 (3.8%)	0	8 (4.3%)	0	16 (4.3%)	0
Nervous System Disorders	**1 (0.6%)**	**1 (0.6%)**	**1 (0.7%)**	**1 (0.7%)**	**1 (0.5%)**	**1 (0.5%)**	**1 (0.5%)**	**1 (0.5%)**	**2 (0.5%)**	**1 (0.3%)**
ICANS	0	1 (0.6%)	0	1 (0.7%)	0	1 (0.5%)	0	1 (0.5%)	0	1 (0.3%)

Abbreviations: B-NHL = B-cell non-Hodgkin lymphoma; DLBCL = diffuse large B-cell lymphoma; ICANS = immune effector cell-associated neurotoxicity syndrome; iNHL = indolent B-cell non-Hodgkin lymphoma; LBCL = large B-cell lymphoma; MCL = mantle cell lymphoma; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SOC = system organ class; TEAE = treatment-emergent adverse event.

Note: Safety Pool 01 includes GCT3013-01. Safety Pool 01+04 includes GCT3013-01 and GCT3013-04. All B-NHL is composed of the LBCL population plus subjects with iNHL (n=128) and MCL (n=38) from the escalation and expansion parts of the trials. Percentages calculated based on N. Sorted by descending frequency in the Safety Pool 01+04 LBCL grade 3-4 column.

Note: Adverse events are classified using MedDRA v24.1 and are counted only once per system organ class and only once per preferred term.

Data cutoff date:31 Jan 2022

Source: Table 3.11, Table 3.12

Adverse events of special interest

Cytokine release syndrome (CRS)

Taking into consideration the anticipated risk of CRS, precautions to minimize the incidence and severity of CRS were implemented in the GCT3013-01 trial including guidelines on management, premedication, prophylactic corticosteroids, hospitalizations, and monitoring. Consistent measures were followed in GCT3013-04. Please refer to the efficacy part for more information on premedication.

The AESI of CRS was analysed and summarised at the subject level and at the event level. In the subject-level analysis, subjects with multiple CRS events were counted only once and may have been counted in more than 1 dosing period. In the event-level analysis, all CRS events are counted, including multiple episodes experienced by the same subject.

Subject level analysis

Safety Pool 01: GCT3013-01 (ESC + EXP)

In the Safety Pool 01 LBCL group (N=167), 84 (50.3%) subjects experienced at least 1 CRS event (Table 59), and the maximum grade was 1 or 2 in 80 of the 84 subjects. Most subjects had a maximum grade 1 event (52 subjects; 31.1%), with 28 (16.8%) subjects having a maximum grade 2 event and 4 (2.4%) subjects having a maximum grade 3 event. No grade 4 or grade 5 events of CRS occurred. Fever was reported in 83 of the 84 subjects, hypotension in 26 of the 84 subjects, and hypoxia in 16 of the 84 subjects.

The highest rate of CRS was reported in association with the first full dose of 48 mg epcoritamab on C1D15 (43.6%; 68 subjects), followed by the intermediate dose on C1D8 (12.9%; 21 subjects) and the priming dose on C1D1 (6.6%; 11 subjects) (Table 58). Seven (4.6%) subjects had a CRS event after the second full dose (C1D22). Almost all CRS events occurred during the first cycle, as only 4 (2.8%) subjects had a CRS event at some point after the third full dose.

A total of 77 (46.1%) subjects with LBCL received a concomitant medication for the treatment of CRS, including tocilizumab in 25 (15.0%) subjects and corticosteroids (beyond those scheduled for CRS prophylaxis) in 18 (10.8%) subjects.

Twelve (7.2%) subjects had CRS that led to dose delay and 1 (0.6%) subject, with prior recurrent CRS, had a grade 1 CRS episode on D116 (in C4) and concomitant grade 3 fatigue in the setting of disease progression that led to treatment discontinuation. All other subjects continued treatment.

The median time to first CRS onset was 16.0 days (range: 1, 55), generally following administration of the first full dose of 48 mg epcoritamab on C1D15 (Table 59). Median time to onset was 17.2 hours (range: 12, 105) from the priming dose, 70.7 hours (range: 12, 213) from the intermediate dose, 19.9 hours (range: 12, 126) from the first full dose, 81.0 hours (range: 19, 86) from the second full dose, and 73.9 hours (range 33, 118) from any subsequent full doses (Table 58). The median time to CRS resolution in the primary GCT3013-01 ESC+EXP R/R LBCL analysis set was 3.0 days (range: 1 to 27 days).

Table 45: Summary of Cytokine Release Syndrome Events by Dosing Period (48 mg Safety Analysis Set – Escalation + Expansion)

Safety Pool 01 LBCL (N=167) Number of Subjects	**Dosing Period**				
	Priming (N=167)	**Intermediate (N=163)**	**First Full (N=156)**	**Second Full (N=151)**	**Third Full and after (N=143)**
Subjects with ≥ 1 CRS event, n (%)	**11 (6.6%)**	**21 (12.9%)**	**68 (43.6%)**	**7 (4.6%)**	**4 (2.8%)**
Grade 1	8 (4.8%)	17 (10.4%)	42 (26.9%)	5 (3.3%)	2 (1.4%)
Grade 2	3 (1.8%)	4 (2.5%)	22 (14.1%)	2 (1.3%)	2 (1.4%)
Grade 3	0	0	4 (2.6%)	0	0
Occurrence of any CRS Signs and Symptoms, , n (%)	**11 (6.6%)**	**21 (12.9%)**	**68 (43.6%)**	**7 (4.6%)**	**4 (2.8%)**
Fever	10	20	68	7	4
Hypotension	2	4	19	2	2
Hypoxia	2	4	11	2	1
Other[a]	2	7	13	1	0
Subject with CRS					
Treated with anti-cytokine therapy	1	5	19	1	2
Tocilizumab	1	5	19	1	2
Other anti-cytokine	0	0	0	0	0
Treated with corticosteroid for CRS	1	3	14	1	1

Leading to dose delay	0	1	8	2	3
Leading to treatment discontinuation	0	0	0	0	1
Time from most recent dosing(hours)					
n	11	21	68	7	4
Mean (SD) [b]	26.6 (26.75)	66.6 (47.54)	30.7 (28.22)	57.9 (31.84)	74.8 (46.27)
Median	17.2	70.7	19.9	81.0	73.9
Minimum, Maximum	12, 105	12, 213	12, 126	19, 86	33, 118

Abbreviations: CRS = cytokine release syndrome; DLBCL = diffuse large B-cell lymphoma; LBCL = large B-cell lymphoma; SD = standard deviation.

Note: CRS events are graded according to (Lee et al 2019). Percentages are based on number of treated subjects in the analysis period. For partial CRS onset time, time to CRS onset will be imputed as 12 hours if CRS onset date falls on the same date as the most recent dosing date, or CRS onset time would be imputed as T00:00 if later than the most recent dosing date. For CRS resolution time, CRS onset and resolution time would be imputed as T00:00 and T23:59, respectively, if time component is missing.

[a] Other includes the following preferred terms: confusional state, dizziness, headache, vomiting, diarrhea, nausea, dyspnea, chills, tremor, arthralgia, tachycardia, sinus tachycardia, C-reactive protein increase, and rash erythematous (GCT3013-01-EXP-aNHL CSR Listing 16.2.7.6).

[b] Based on the first CRS in subjects with >1 CRS event within the dosing period.

[c] Percentage calculated based on subjects with at least 1 CRS event.

Data cutoff date: 31 Jan 2022

Source: Table 5.2

Safety Pool 01+04: GCT3013-01 (ESC + EXP) + GCT3013-04 (ESC + EXP)

In the Safety Pool 01+04 LBCL group (N=208), 119 (57.2%) subjects experienced at least 1 CRS event (Table 59), and the maximum grade event was grade 1 or 2 in 111 of the 119 subjects. Most subjects had a maximum grade 1 event (72 subjects; 34.6%), with 39 (18.8%) subjects having a maximum grade 2 event and 8 (3.8%) subjects having a maximum grade 3 event. No grade 4 or grade 5 events of CRS occurred. Fever was reported in 118 of the 119 subjects, hypotension in 38 of the 119 subjects, and hypoxia in 24 of the 119 subjects.

The highest rate of CRS was reported in association with the first full dose of 48 mg epcoritamab on C1D15 (49.0%; 96 subjects), followed by the intermediate dose on C1D8 (15.8%; 32 subjects) and the priming dose on C1D1 (9.6%; 20 subjects). Fifteen (7.9%) subjects had a CRS event after the second full dose (C1D22). Almost all CRS events occurred during the first cycle, as only 9 (5.0%) subjects had a CRS event at some point after the third full dose (C2D1).

A total of 109 (52.4%) subjects with LBCL received a concomitant medication for the treatment of CRS, including tocilizumab in 37 (17.8%) subjects and corticosteroids (beyond those scheduled for CRS prophylaxis) in 33 (15.9%) subjects.

Fifteen (7.2%) subjects had CRS that led to dose delay and in 1 (0.5%) subject, with prior recurrent CRS, grade 1 CRS and concomitant grade 3 fatigue in the setting of disease progression led to treatment discontinuation.

The median time to first CRS onset was 16.0 days (range: 1, 55), generally following administration of the first full dose of 48 mg epcoritamab on C1D15 (Table 59). In the 96 subjects who experienced CRS after the first full dose, the median time to onset from the last epcoritamab injection was 20.0 hours (range: 12, 126). Median time to onset was 19.1 hours (range: 12, 133) from the priming dose, 67.7 hours (range: 12, 213) from the intermediate dose, 20.0 hours (range: 12, 126) from the first full dose, 86.0 hours (range: 19, 133) from the second full dose, and 33.4 hours (range 12, 118) from any subsequent full doses.

In the Safety Pool 01+04 All B-NHL group (N=374), 230 (61.5%) subjects experienced at least 1 CRS event (Table 59), and maximum grade event was grade 1 or 2 in 214 of the 230 subjects. Most subjects had a maximum grade 1 event (135 subjects; 36.1%), with 79 (21.1%) subjects having a

maximum grade 2 event, 15 (4.0%) subjects having a maximum grade 3 event, and 1 (0.3%) subject having a maximum grade 4 event. No grade 5 events of CRS occurred. Fever was reported in 229 of the 230 subjects, hypotension in 76 of the 230 subjects, and hypoxia in 43 of the 230 subjects.

Consistent with the pooled LBCL subjects, the highest rate of CRS was reported in association with the first full dose of 48 mg epcoritamab on C1D15 (54.8%; 193 subjects), followed by the intermediate dose (15.5%; 56 subjects) and the priming dose (12.3%; 46 subjects). Almost all CRS events occurred during the first cycle, as only 17 (5.3%) subjects had a CRS event at some point after the third full dose.

A total of 211 (56.4%) subjects with LBCL received a concomitant medication for the treatment of CRS, including tocilizumab in 80 (21.4%) subjects and corticosteroids (beyond those scheduled for CRS prophylaxis) in 61 (16.3%) subjects.

The most common concomitant treatments received (other than for prophylaxis) were paracetamol (169 subjects), tocilizumab (80 subjects), sodium chloride (53 subjects), oxygen (43 subjects), piperacillin sodium + tazobactam sodium (30 subjects), dexamethasone (24 subjects), solutions affecting the electrolyte balance (22 subjects), and prednisolone (16 subjects).

Twenty-nine (7.8%) subjects had CRS that led to dose delay and in 2 (0.5%) subjects CRS led to treatment discontinuation. One of the subjects had CRS (grade 1) with concomitant grade 3 fatigue in the setting of disease progression that led to treatment discontinuation as described above. The other subject was in the GCT3013-01 MCL expansion cohort and had CRS that was grade 4 in the context of progressive disease. The CRS was ongoing at the time of treatment withdrawal.

The median time to first CRS onset was 16.0 days (range: 1, 59), generally following administration of the first full dose of 48 mg epcoritamab on C1D15 (Table 59). Median time to onset was 17.2 hours (range: 12, 165) from the priming dose, 38.8 hours (range: 12, 213) from the intermediate dose, 18.7 hours (range: 12, 130) from the first full dose, 82.8 hours (range: 12, 133) from the second full dose, and 13.1 hours (range 12, 135) from any subsequent full doses. The median time to CRS resolution was 3.0 days (range: 1 to 36 days).

Table 46: Summary of AESI: Cytokine Release Syndrome (48 mg Safety Analysis Set – Escalation + Expansion)

	Safety Pool 01		Safety Pool 01+04		
	LBCL (N=167)	DLBCL (N=148)	LBCL (N=208)	DLBCL (N=188)	All B-NHL (N=374)
Subjects with ≥1 CRS event, n (%)	**84 (50.3%)**	**73 (49.3%)**	**119 (57.2%)**	**107 (56.9%)**	**230 (61.5%)**
Grade 1	52 (31.1%)	45 (30.4%)	72 (34.6%)	65 (34.6%)	135 (36.1%)
Grade 2	28 (16.8%)	24 (16.2%)	39 (18.8%)	34 (18.1%)	79 (21.1%)
Grade 3	4 (2.4%)	4 (2.7%)	8 (3.8%)	8 (4.3%)	15 (4.0%)
Grade 4	0	0	0	0	1 (0.3%)
Occurrence of any CRS Signs and Symptoms, n (%)	**84 (50.3%)**	**73 (49.3%)**	**119 (57.2%)**	**107 (56.9%)**	**230 (61.5%)**
Fever	83	72	118	106	229 (61.2%)
Hypotension	26	24	38	36	76 (20.3%)
Hypoxia	16	14	24	21	43 (11.5%)
Other[a]	19	18	24	23	63 (16.8%)
Subjects with CRS, n (%)					
Treated with anti-cytokine therapy	25 (15.0%)	21 (14.2%)	37 (17.8%)	33 (17.6%)	81 (21.7%)
Tocilizumab	25 (15.0%)	21 (14.2%)	37 (17.8%)	33 (17.6%)	80 (21.4%)
Other anti-cytokine	0	0	0	0	1 (0.3%)
Treated with corticosteroid for CRS	18 (10.8%)	14 (9.5%)	33 (15.9%)	29 (15.4%)	60 (16.0%)

Leading to dose delay	12 (7.2%)	8 (5.4%)	15 (7.2%)	11 (5.9%)	29 (7.8%)
Leading to treatment discontinuation	1 (0.6%)	1 (0.7%)	1 (0.5%)	1 (0.5%)	2 (0.5%)
Time to first CRS onset (days)					
n	84	73	119	107	230
Mean (SD)	14.5 (7.37)	13.8 (6.06)	13.9 (7.13)	13.4 (6.10)	13.8 (8.22)
Median	16.0	16.0	16.0	16.0	16.0
Minimum, Maximum	1, 55	1, 31	1, 55	1, 31	1, 59

Abbreviations: AESI = adverse event of special interest; CRS = cytokine release syndrome; DLBCL = diffuse large B-cell lymphoma; iNHL = indolent B-cell non-Hodgkin lymphoma; LBCL = large B-cell lymphoma; MCL = mantle cell lymphoma; SD = standard deviation.

Note: Safety Pool 01 includes GCT3013-01. Safety Pool 01+04 includes GCT3013-01 and GCT3013-04. All B-NHL is composed of the LBCL population plus subjects with iNHL (n=128) and MCL (n=38) from the escalation and expansion parts of the trials.

Note: CRS events are graded according to (Lee et al 2019).

[a] Other includes the following preferred terms: confusional state, dizziness, headache, vomiting, diarrhea, nausea, dyspnea, chills, tremor, arthralgia, tachycardia, sinus tachycardia, C-reactive protein increase, and rash erythematous (GCT3013-01-EXP-aNHL CSR Listing 16.2.7.6).

Data cutoff date:31 Jan 2022

Source: Table 5.1

Event level analysis

Safety Pool 01: GCT3013-01 (ESC + EXP)

In the Safety Pool 01 LBCL group (N=167), a total of 123 CRS events were reported in 84 subjects (Table 60). Among these 84 subjects, 56 (66.7%) subjects had 1 CRS episode, 20 (23.8%) subjects had 2 CRS episodes, 6 (7.1%) subjects had 3 CRS episodes, 1 (1.2%) subject had 4 CRS episodes, and 1 (1.2%) subject had 5 CRS episodes. Most of the 123 CRS events were maximum grade 1 (84 events; 68.3%), with 35 (28.5%) maximum grade 2 events and 4 (3.3%) maximum grade 3 events. Fever was reported as a symptom of CRS in 121 (98.4%) of the total 123 events, hypotension in 30 (24.4%) events, and hypoxia in 21 (17.1%) events.

Most CRS events occurred during the first cycle of treatment, with the highest number of CRS events reported in association with the first full dose of 48 mg epcoritamab on C1D15 (74 events in 68 subjects), followed by the intermediate dose on C1D8 (21 events in 21 subjects) and the priming dose on C1D1 (12 events in 11 subjects). Eight CRS events occurred in 7 subjects after the second full dose (C1D22). Almost all CRS events occurred during the first cycle, as only 8 events occurred in 4 subjects after the third full dose on C2D1 and thereafter.

Tocilizumab was administered to treat 31 (25.2%) of the 123 CRS events and corticosteroids (beyond those scheduled for prophylaxis) for 20 (16.3%) of the events (Table 60). Fourteen (11.4%) CRS events led to dose delay and 1 (0.8%) grade 1 CRS event with concomitant grade 3 fatigue in the setting of disease progression led to treatment discontinuation.

The median time to CRS onset from most recent dosing was 2.0 days (range: 1, 11) (Table 60). The median time to onset was 19.1 hours (range: 12, 108) after priming, 70.7 hours (range: 12, 213) after intermediate dose, 20.6 hours (range: 12, 161) after the first full dose, 81.0 hours (range: 19, 171) after the second full dose, and 58.4 hours (range: 12, 239) following any subsequent full doses. Median times to CRS resolution were 26.7, 48.0, 48.0, 72.0, and 28.3 hours, respectively.

At data cutoff, 121 (98.4%) of the 123 CRS events achieved resolution with median time to resolution of 2.0 days (range: 1, 27). Of the 2 unresolved cases, 1 was the grade 1 CRS concurrent with grade 3 fatigue that led to treatment discontinuation mentioned above. The second unresolved CRS case was in a subject who had 2 episodes of CRS. The first episode of Grade 3 CRS occurred at C1D15, resolved on Day 19 and epcoritamab was delayed. The second CRS event (Grade 2) in this patient occurred at

C1D22 (administered at D36) with concurrent disease progression. No further CRS treatment was given and the patient died due to disease progression at D46.

Safety Pool 01+04: GCT3013-01 (ESC + EXP) + GCT3013-04 (ESC + EXP)

In the Safety Pool 01+04 LBCL group (N=208), a total of 192 CRS events were reported in 119 subjects (Table 60). Among these 119 subjects, 74 (62.2%) subjects had 1 CRS episode, 25 (21.0%) subjects had 2 CRS episodes, 15 (12.6%) subjects had 3 CRS episodes, 2 (1.7%) subjects had 4 CRS episodes, and 3 (2.5%) subjects had 5 CRS episodes. Most of the 192 CRS events were maximum grade 1 (131 events; 68.2%), with 53 (27.6%) maximum grade 2 events and 8 (4.2%) maximum grade 3 events. Fever was reported as a symptom of CRS in 187 (97.4%) of the total 192 events, hypotension in 45 (23.4%) of the events, and hypoxia in 33 (17.2%) of the events.

Most CRS events occurred during the first cycle of treatment, with the highest number of CRS events reported in association with the first full dose of 48 mg epcoritamab on C1D15 (105 events in 96 subjects), followed by the intermediate dose on C1D8 (33 events in 32 subjects) and the priming dose on C1D1 (22 events in 20 subjects). Sixteen events occurred in 15 subjects after the second full dose. Almost all CRS events occurred during the first cycle, as 16 events occurred in 9 subjects following the third full dose on C2D1 and thereafter.

Tocilizumab was administered to treat 46 (24.0%) of the 192 events and corticosteroids (beyond those scheduled for prophylaxis) for 41 (21.4%) of the events (Table 60). Eighteen (9.4%) CRS events led to dose delay and 1 (0.5%) grade 1 CRS event with concomitant grade 3 fatigue in the setting of disease progression led to treatment discontinuation.

The median time to CRS onset from most recent dosing was 2.0 days (range: 1, 11) (Table 60). The median time to onset was 21.3 hours (range: 12, 147) after priming, 70.7 hours (range: 12, 213) after intermediate dose, 21.0 hours (range: 12, 161) after the first full dose, 94.0 hours (range: 19, 171) after the second full dose, and 34.2 hours (range: 12, 239) following any subsequent full doses. Median times to CRS resolution were 37.0, 48.0, 48.0, 43.7, and 32.6 hours, respectively.

As of the data cutoff date, 190 (99.0%) of the 192 CRS events achieved resolution. The 2 unresolved cases were ongoing at the time of each of the subject's death, as described above.

In the aNHL cohort of the GCT3013-01 study expansion part, the majority of CRS events (69/112 events, 61.6%) occurred outside of the mandatory 24-hours hospitalization period. 43 CRS events (38.4%) occurred within the 24 hours mandatory hospitalization period (after the first full dose). There were four Grade 3 CRS events and all began within 24 hours of the 1st full dose. In 3 of the 4 cases, CRS started with a lower grade and developed to a Grade 3 event, which was already being managed accordingly. Half of the subjects (79/157, 50.3%) did not experience any CRS event.

In the Safety Pool 01+04 All B-NHL group (N=374), a total of 377 CRS events were reported in 230 subjects (Table 60). Among these 230 subjects, 140 (60.9%) subjects had 1 CRS episode, 50 (21.7%) subjects had 2 CRS episodes, 28 (12.2%) subjects had 3 CRS episodes, 8 (3.5%) subjects had 4 CRS episodes, 3 (1.3%) subjects had 5 CRS episodes, and 1 (0.4%) subject had 6 CRS episodes. Most of the 377 CRS events were maximum grade 1 (252 events; 66.8%), with 109 (28.9%) maximum grade 2 events, 15 (4.0%) maximum grade 3 events, and 1 (0.3%) maximum grade 4 event. Fever was reported as a symptom of CRS in 371 (98.4%) of the total 377 events, hypotension in 91 (24.1%) of the events, and hypoxia in 58 (15.4%) of the events.

Most CRS events occurred during the first cycle of treatment, with the highest number of CRS events reported in association with the first full dose of 48 mg epcoritamab on C1D15 (214 events in 193 subjects) followed by the intermediate dose on C1D8 (58 events in 56 subjects) and the and the priming dose on C1D1 (48 events in 46 subjects). Twenty-nine events occurred in 26 subjects after the

second full dose (C1D22). Twenty-eight CRS events occurred in 17 subjects after the third full dose on C2D1 and thereafter.

Tocilizumab was administered in 99 (26.3%) of the 377 events and corticosteroids (beyond those scheduled for prophylaxis) in 76 (20.2%) of the events (Table 60). Thirty-four (9.0%) CRS events led to dose delay and 2 (0.5%) events led to treatment discontinuation. One of the events leading to discontinuation was a grade 1 event in an LBCL subject from GCT3013-01, who had concurrent grade 3 fatigue and disease progression (as described above). The other CRS event that led to treatment discontinuation was a grade 4 CRS event in an MCL subject who died from disease progression.

The median time to CRS onset from most recent dosing was 2.0 days (range: 1, 12) (Table 60). The median time to onset was 17.8 hours (range: 12, 165) after the priming dose, 41.8 hours (range: 12, 213) after the intermediate dose, 19.9 hours (range: 12, 161) after the first full dose, 83.1 hours (range: 12, 253) after the second full dose, and 35.1 hours (range: 12, 251) following any subsequent full doses. Median times to CRS resolution were 26.7, 31.4, 48.0, 47.1, and 29.0 hours, respectively.

At data cutoff, 372 (98.7%) of the 377 CRS events achieved resolution (Table 60). Two of the unresolved CRS events occurred after the first full dose and 3 occurred after the second full dose. In addition to the 2 LBCL subjects with unresolved CRS events described above, there was a subject with FL with no entry in the CRF for outcome of the CRS event but a defined end date in the AE listing, who discontinued treatment due to declining health; an MCL subject with grade 4 CRS concurrent with multiple organ failure that led to discontinuation of study treatment followed by death due to disease progression; and an MCL subject whose CRS onset date was the day before the data cut-off.

Table 47: Event-Level Cytokine Release Syndrome Summary (48 mg Safety Analysis Set – Escalation + Expansion)

	Safety Pool 01		**Safety Pool 01+04**		
	LBCL (N=167)	**DLBCL (N=148)**	**LBCL (N=208)**	**DLBCL (N=188)**	**All B-NHL (N=374)**
Subjects with ≥1 CRS event, n (%)	**84**	**73**	**119**	**107**	**230**
Number of episodes per subject [a]					
1 event	56 (66.7%)	49 (67.1%)	74 (62.2%)	66 (61.7%)	140 (60.9%)
2 events	20 (23.8%)	16 (21.9%)	25 (21.0%)	21 (19.6%)	50 (21.7%)
3 events	6 (7.1%)	6 (8.2%)	15 (12.6%)	15 (14.0%)	28 (12.2%)
4 events	1 (1.2%)	1 (1.4%)	2 (1.7%)	2 (1.9%)	8 (3.5%)
5 events	1 (1.2%)	1 (1.4%)	3 (2.5%)	3 (2.8%)	3 (1.3%)
6 events	0	0	0	0	1 (0.4%)
Number of CRS events	123	108	192	176	377
Grade 1	84 (68.3%)	74 (68.5%)	131 (68.2%)	121 (68.8%)	252 (66.8%)
Grade 2	35 (28.5%)	30 (27.8%)	53 (27.6%)	47 (26.7%)	109 (28.9%)
Grade 3	4 (3.3%)	4 (3.7%)	8 (4.2%)	8 (4.5%)	15 (4.0%)
Grade 4	0	0	0	0	1 (0.3%)
Occurrence of any CRS Signs and Symptoms, n (%)	**123 (100.0%)**	**108 (100.0%)**	**192 (100.0%)**	**176 (100.0%)**	**377 (100.0%)**
Fever	121 (98.4%)	106 (98.1%)	187 (97.4%)	171 (97.2%)	371 (98.4%)
Hypotension	30 (24.4%)	27 (25.0%)	45 (23.4%)	42 (23.9%)	91 (24.1%)
Hypoxia	21 (17.1%)	19 (17.6%)	33 (17.2%)	30 (17.0%)	58 (15.4%)
Other[b]	24 (19.5%)	23 (21.3%)	30 (15.6%)	29 (16.5%)	80 (21.2%)
CRS event, n (%)					
Treated with anti-cytokine therapy	31 (25.2%)	27 (25.0%)	46 (24.0%)	42 (23.9%)	100 (26.5%)
Tocilizumab	31 (25.2%)	27 (25.0%)	46 (24.0%)	42 (23.9%)	99 (26.3%)
Other anti-cytokine	0	0	0	0	1 (0.3%)
Treated with corticosteroid for CRS	20 (16.3%)	14 (13.0%)	41 (21.4%)	35 (19.9%)	76 (20.2%)

Leading to dose delay	14 (11.4%)	9 (8.3%)	18 (9.4%)	13 (7.4%)	34 (9.0%)
Leading to treatment discontinuation	1 (0.8%)	1 (0.9%)	1 (0.5%)	1 (0.6%)	2 (0.5%)
Time to CRS onset from most recent dosing (days)					
n	123	108	192	176	377
Mean (SD)	3.1 (1.89)	3.0 (1.85)	3.2 (1.87)	3.1 (1.85)	3.0 (1.98)
Median	2.0	2.0	2.0	2.0	2.0
Minimum, Maximum	1, 11	1, 11	1, 11	1, 11	1, 12
Time to CRS Resolution (days)					
Resolved CRS, n (%)	121 (98.4%)	106 (98.1%)	190 (99.0%)	174 (98.9%)	372 (98.7%)
Mean (SD)	3.1 (3.14)	2.9 (2.15)	3.4 (3.38)	3.2 (2.59)	3.4 (3.80)
Median	2.0	2.0	2.0	2.0	2.0
Minimum, Maximum	1, 27	1, 15	1, 27	1, 15	1, 36

Abbreviations: B-NHL = B-cell non-Hodgkin lymphoma; CRS = cytokine release syndrome; DLBCL = diffuse large B-cell lymphoma; iNHL = indolent B-cell non-Hodgkin lymphoma; LBCL = large B-cell lymphoma; MCL = mantle cell lymphoma; SD = standard deviation.

Note: Safety Pool 01 includes GCT3013-01. Safety Pool 01+04 includes GCT3013-01 and GCT3013-04. All B-NHL is composed of the LBCL population plus subjects with iNHL (n=128) and MCL (n=38) from the escalation and expansion parts of the trials.

Note: CRS events are graded according to (Lee et al 2019).

[a] Percentage calculated based on number of subjects with at least 1 CRS event. Other percentages are calculated based on number of CRS events in the analysis group.

[b] Other includes the following preferred terms: ataxia, confusional state, dizziness, headache, vomiting, diarrhea, nausea, dyspnea, chills, tremor, arthralgia, tachycardia, sinus tachycardia, C-reactive protein increase, and rash erythematous (GCT3013-01-EXP-aNHL CSR Listing 16.2.7.6).

Data cutoff date:31 Jan 2022

Source: Table 5.3

Evaluation of tocilizumab use in CRS management

Safety Pool 01+04 All B-NHL Group: In the Safety Pool 01+04 All B-NHL group (N = 374), a total of 377 CRS events of any grade were reported, and 99 (26.3%) of these events were managed by tocilizumab treatment.

Among the 377 CRS events, most were grade 1 (252, 66.8%) or grade 2 (109, 28.9%), with 15 (4.0%) events grade 3, and 1 (0.3%) grade 4, per the ASTCT criteria. Among the 99 CRS events where tocilizumab was administered, 19 (19.2%) were grade 1, 64 (64.6%) were grade 2, 15 (15.2%) were grade 3, and 1 (1.0%) was grade 4.

Among all treatment-emergent CRS events, most (92.5%) of the grade 1 events were not treated with tocilizumab, while the majority of grade 2 (58.7%) and all (100%) grade 3 and 4 events were treated with tocilizumab. This is generally consistent with the protocol recommendation that tocilizumab be used to treat grade 3 or 4 CRS as well as grade 1 and 2 CRS in an older subject or subject with extensive comorbidities.

An evaluation of the effectiveness of tocilizumab in treating CRS was performed by defining response to tocilizumab as meeting all the following criteria:

- CRS resolution within 4 days following tocilizumab administration, AND
- No new corticosteroids use initiated, AND
- The prophylactic corticosteroid dose as per protocol not escalated.

Based on the above definition for response to tocilizumab, among the 99 CRS events with tocilizumab administration, the majority (79, 79.8%) responded to tocilizumab. The tocilizumab response rate was 89.5%, 84.4%, and 53.3% for CRS of grade 1, 2, and 3, respectively. Of note there was only 1 grade 4 CRS event unresponsive to tocilizumab.

There were 20 (20.2%) CRS events with tocilizumab administration that did not meet the response criteria above and were defined as tocilizumab "failures". The reason(s) for tocilizumab "failure" include(s):

- 13 CRS events did not resolve within 4 days following tocilizumab administration,
- 2 CRS events had a "new" corticosteroid initiated,
- 8 CRS events in which the prophylactic corticosteroid dose was escalated.

Of note, 3 of the CRS events "failed" for more than one reason.

Of the 20 CRS events that "failed" to respond to tocilizumab, half (n = 10: 3 in aNHL subjects, 3 in iNHL subjects, and 4 in MCL subjects) were followed by new corticosteroid initiation (n = 2) or escalation of prophylactic corticosteroid dose (n = 8). Three of the 10 CRS events did not resolve within 4 days following tocilizumab administration, thus meeting 2 criteria for "failure." Therefore, 7 CRS events that did not respond to tocilizumab were considered to have "failed" solely due to additional steroid use. Of these 7 CRS events, 2 events were experienced concurrently with ICANS events as an indication for additional corticosteroid treatment, and 1 event was experienced in a subject whose corticosteroid dose was escalated due to concomitant mild renal impairment, according to the investigator.

Among all 377 CRS events, 372 (98.7%) were resolved by the data cutoff. For all resolved CRS events, the median time to resolution was 3 days for CRS events with tocilizumab administration, and 2 days for CRS events without tocilizumab administration. This difference may reflect that tocilizumab administration was more frequent in managing higher grade CRS events, which may have a longer time to resolution according to the applicant.

Safety Pool 01 LBCL Group: In the Safety Pool 01 LBCL group (N = 167), a total of 123 CRS events of any grade were reported, and 31 (25.2%) of these events were managed by tocilizumab treatment.

Among the 123 CRS events, most were grade 1 (84, 68.3%) or grade 2 (35, 28.5%), with 4 (3.3%) events grade 3, and none grade 4, per the ASTCT criteria. Among the 31 CRS events where tocilizumab was administered, 5 (16.1%) were grade 1, 22 (71.0%) were grade 2, and 4 (12.9%) were grade 3.

Among all treatment-emergent CRS events, most (94.0%) of the grade 1 events were not treated with tocilizumab, while the majority of grade 2 (62.9%) and all (100%) grade 3 events were treated with tocilizumab.

Based on the definition for response to tocilizumab, among the 31 CRS events with tocilizumab administration, the majority (27, 87.1%) responded to tocilizumab. The tocilizumab response rate was 80.0%, 90.9%, and 75.0% for CRS of grade 1, 2, and 3, respectively.

There were 4 (12.9%) CRS events with tocilizumab administration that did not meet the response criteria and were defined as tocilizumab "failures". For all 4 CRS events, the event did not resolve within 4 days following tocilizumab administration. Also, for 2 of the CRS events, the planned prophylactic corticosteroid was administered following the CRS event, but the corticosteroid dose was increased as compared to the protocol-specified prophylactic dose (thus meeting 2 criteria for "failure").

Among all 123 CRS events, 121 (98.4%) were resolved by the data cutoff date. For all resolved CRS events, the median time to resolution was 2 days for CRS events with tocilizumab administration, and 2 days for CRS events without tocilizumab administration.

In addition to tocilizumab and corticosteroids, other concomitant medications were used to treat CRS, such as antipyretics, antibiotics, and intravenous fluids. The most common other therapies

(administered to ≥5% of patients) for CRS were paracetamol, sodium chloride (saline), oxygen, piperacillin sodium;tazobactam sodium, and solutions affecting the electrolyte balance. These medications were mostly administered during the Week ≤8 period.

Preliminary data from the step-up dosing optimization part GCT3013-01

Preliminary supportive data from the step-up dosing (SUD) optimization part of the ongoing GCT3013-01 trial (Protocol Amendment 9/Version 11.0 [07 July 2022]) is provided. In the SUD Optimization Cohort, following administration of the 1st full dose on Cycle 1 Day 15, investigators were given the option to either:

- Proactively hospitalize the subject (e.g., if perceived to have increased risk of severe CRS), OR
- Require the subject to remain in close proximity to the treatment facility (defined as within 30 minutes) for 24 hours after the first full dose of epcoritamab (ie,“"outpatient”" monitoring).

To minimize CRS during treatment with epcoritamab in Cycle 1, strong recommendations were also implemented in the study for proper hydration and use of dexamethasone (15 mg), instead of prednisolone or other corticosteroid equivalent, as the prophylactic corticosteroid administered.

As of the data snapshot date of 08 Mar 2023, 19 subjects with R/R DLBCL across Arms A, B and C received at least 1 dose of epcoritamab (Table 61). Of the 18 subjects who had received the first full dose of epcoritamab, 11 subjects (61.1%) received the first full dose without proactive hospitalization and none of these subjects had CRS following the first full dose (Table 61). Of the 7 subjects with DLBCL who were proactively hospitalized at the time of the first full dose, 2 subjects (28.6%) experienced Grade 1 CRS. It should be noted that 1 of the 7 subjects was hospitalized for peripheral edema prior to the first full dose and subsequently received the first full dose of epcoritamab in the hospital.

Table 48: Summary of Hospitalization and CRS After the First Full Dose of Epcoritamab – GCT3013-01 Optimization Part, DLBCL Cohort (Safety Analysis Set)

Number of Subjects, n (%)	Subjects in DLBCL Cohort[a]
Subjects received any dose of epcoritamab	19
Subjects received the first full dose	18 (94.7%)
Subjects proactively hospitalized for administration of the first full dose[b,c]	7 (38.9%)
Subjects with CRS after the first full dose	2 (28.6%)
Subjects **not** proactively **hospitalized** for administration of the first full dose[b]	11 (61.1%)
Subjects with CRS after the first full dose	0

CRS = cytokine release syndrome; DLBCL= diffuse large B-cell lymphoma.
Note: CRS events were graded according to Lee et al., 2019.[10]
a. DLBCL cohort includes 11 subjects from Arm A (reference; SUD 0.16/0.8/48 mg), 5 subjects from Arm B (SUD 0.32/1.6/48 mg), and 3 subjects from Arm C (SUD 0.64/3/48 mg). The first full dose of epcoritamab was administered on Cycle 1 Day 15.
b. Percentage calculated based on subjects who received the first full dose of epcoritamab.
c. One subject was hospitalized due to another adverse event and was in the hospital during administration of the first full dose of epcoritamab.
Data snapshot date: 08 Mar 2023 (preliminary data) Source: Table ir15.q1.dlbcl.a

CRS incidence, severity, hospitalization, treatment, and outcome during Cycle 1 are summarized in Table 62. The applicant evaluated CRS throughout Cycle 1, which included any CRS events that occurred following priming, intermediate, or full doses of epcoritamab.

Most subjects did not experience CRS following the first full dose of epcoritamab. Of the 5 subjects with DLBCL who had CRS, CRS occurred after the priming dose in 3 subjects, after the intermediate dose in 1 subject, and after the first full dose in 2 subjects (in one subject, the CRS occurred more than 24 hours post-dose). The main symptom experienced by subjects with grade 1 CRS was fever (5 subjects; 100%). Importantly CRS resolved in all 5 subjects, with a median time to resolution of 4 days (range: 1, 6). No subjects discontinued epcoritamab treatment due to CRS. One subject had a dose delay due to CRS.

As per protocol recommendations, nearly all subjects in the optimization part received additional hydration (oral and intravenous) and primarily used dexamethasone as CRS prophylaxis, and data suggest that these mitigation strategies contribute to a lower incidence and severity of CRS.

Additionally, the CRS data from the 11 subjects in Arm A who received the same step-up dosing regimen as the expansion part of the GCT3013-01 trial (i.e. 0.16 mg priming/ 0.8 mg intermediate/ 48 mg full dose) are consistent with that of all 19 DLBCL subjects from the SUD optimization part of the GCT3013-01 trial.

Table 49: Summary of Cytokine Release Syndrome During Cycle 1 – GCT3013-01 Optimization Part, DLBCL Cohort (Safety Analysis Set)

Number of Subjects, n (%)	Subjects in DLBCL Cohort[a] (N=19)
Subjects with ≥1 CRS event	5 (26.3%)
Grade 1	5 (26.3%)
Grade 2	0
Grade 3	0
Grade 4	0
Grade 5	0
Subjects with hospitalization due to CRS	3 (15.8%)
Occurrence of any CRS signs and symptoms[c]	5 (100%)
Fever	5 (100%)
Hypotension	0
Hypoxia	0
Other[b]	2 (40.0%)
Subjects with CRS[d]	
Treated with anti-cytokine therapy	1 (20.0%)
Tocilizumab	1 (20.0%)
Other anti-cytokine	0
Treated with corticosteroid for CRS	0
Leading to dose delay/interruption	1 (20.0%)
Leading to treatment discontinuation	0
Time to CRS resolution (days)	
Subjects with resolved CRS[e]	5 (100%)
Mean (SD)[d]	3.8 (1.92)
Median	4.0
Min, Max	1, 6

CRS = cytokine release syndrome; DLBCL= diffuse large B-cell lymphoma; max = maximum; min = minimum; SD = standard deviation.
Note: CRS events were graded according to Lee et al., 2019.[10] a.

DLBCL cohort includes 11 subjects from Arm A (reference; SUD 0.16/0.8/48 mg), 5 subjects from Arm B (SUD 0.32/1.6/48 mg), and 3 subjects from Arm C (SUD 0.64/3.0 mg). The first full dose of epcoritamab was administered on Cycle 1 Day 15.
b. Other includes the following preferred terms: dizziness, dyspnea, headache, pain, and tachycardia
c. Percentage calculated based on subjects with at least 1 CRS event.
d. Based on longest recorded CRS duration in subjects with >1 CRS event.
Data snapshot date: 08 Mar 2023 (preliminary data) Source: Table ir15.q1.dlbcl

Immune effector-cell associated neurotoxicity syndrome (ICANS)

In the Dose Escalation Part of the GCT3013-01 trial, neurological assessment was conducted according to the CARTOX-10 scale (Neelapu et al., 2017). In the Expansion Parts of the GCT3013-01 and GCT3013-04 trials, ICANS events were graded according to ASTCT criteria (Lee et al, 2019). Symptoms of ICANS may include aphasia, altered level of consciousness, impairment of cognitive skills, motor weakness, seizures, and cerebral edema (Lee et al, 2019). Overall, the ICANS grade was determined by the most severe event of the neurotoxicity domains (ICE score, level of consciousness, seizure, motor findings, raised intracranial pressure/cerebral edema) not attributable to any other cause.

Safety Pool 01: GCT3013-01 (ESC + EXP)

In the Safety Pool 01 LBCL group (N=167), 10 (6.0%) subjects experienced ICANS (Table 63). In 7 subjects, the ICANS overlapped with CRS events. Median time to first ICANS onset was 16.5 days (range: 8, 141). All of the events were considered treatment-related, and most were grade 1 (4.2%; 7 subjects) or grade 2 (1.2%; 2 subjects) events. There were no grade 3 or 4 ICANS events.

One (0.6%) subject had a fatal ICANS event (grade 5). The fatal episode of ICANS, in a 70-80-year-old female subject with DLBCL, was an on-treatment event with onset on D12, 5 days after the subject's most recent dose of study drug (0.8 mg intermediate dose), was considered to be related to study drug, and led to treatment discontinuation. Further details on the fatal event of ICANS can be found in the discussion regarding fatal TEAEs.

Except for the grade 5 case, all other episodes of ICANS resolved (90.0%; 9/10 subjects) with supportive care, dose delay in 3 (1.8%) subjects, and/or dexamethasone or other treatments. Median time to resolution was 5.0 days (range: 1, 9). One in 167 treated subjects (0.6%), the fatal event discussed above, discontinued treatment due to ICANS (Table 63).

Safety Pool 01+04: GCT3013-01 (ESC + EXP) + GCT3013-04 (ESC + EXP)

The profile of ICANS events (Table 63) were similar to that reported above for Safety Pool 01.

Table 50: Summary of AESI: Immune Effector Cell-Associated Neurotoxicity Syndrome (48 mg Safety Analysis Set – Escalation + Expansion)

	Safety Pool 01		Safety Pool 01+04		
	LBCL (N=167)	DLBCL (N=148)	LBCL (N=208)	DLBCL (N=188)	All B-NHL (N=374)
Subjects with ≥1 ICANS event, n (%)	**10 (6.0%)**	**9 (6.1%)**	**11 (5.3%)**	**10 (5.3%)**	**23 (6.1%)**
Grade 1	7 (4.2%)	6 (4.1%)	8 (3.8%)	7 (3.7%)	16 (4.3%)
Grade 2	2 (1.2%)	2 (1.4%)	2 (1.0%)	2 (1.1%)	6 (1.6%)
Grade 3	0	0	0	0	0
Grade 4	0	0	0	0	0
Grade 5	1 (0.6%)	1 (0.7%)	1 (0.5%)	1 (0.5%)	1 (0.3%)
Worst On-treatment ICE score, n (%)					
10	3 (1.8%)	2 (1.4%)	3 (1.4%)	2 (1.1%)	4 (1.1%)
7-9	5 (3.0%)	5 (3.4%)	6 (2.9%)	6 (3.2%)	14 (3.7%)
3-6	1 (0.6%)	1 (0.7%)	1 (0.5%)	1 (0.5%)	4 (1.1%)
0-2	0	0	0	0	0

	Safety Pool 01		Safety Pool 01+04		
	LBCL (N=167)	DLBCL (N=148)	LBCL (N=208)	DLBCL (N=188)	All B-NHL (N=374)
Missing	1 (0.6%)	1 (0.7%)	1 (0.5%)	1 (0.5%)	1 (0.3%)
Subjects with ICANS event, n (%)					
Leading to dose delay	3 (1.8%)	3 (2.0%)	3 (1.4%)	3 (1.6%)	5 (1.3%)
Leading to treatment discontinuation	1 (0.6%)	1 (0.7%)	1 (0.5%)	1 (0.5%)	1 (0.3%)
Time to first ICANS onset (days)					
n	10	9	11	10	23
Mean (SD)	29.0 (39.60)	30.4 (41.72)	26.8 (38.25)	27.9 (40.15)	25.7 (28.54)
Median	16.5	17.0	16.0	16.5	16.0
Minimum, Maximum	8, 141	8, 141	5, 141	5, 141	5, 141
Time to ICANS Resolution (days)					
Subjects with resolved ICANS [a]	9 (90.0%)	8 (88.9%)	10 (90.9%)	9 (90.0%)	22 (95.7%)
Mean (SD) [b]	5.0 (3.77)	4.5 (3.70)	4.8 (3.61)	4.3 (3.50)	3.7 (3.06)
Median	5.0	3.5	4.0	3.0	2.0
Minimum, Maximum	1, 9	1, 9	1, 9	1, 9	1, 9

Abbreviations: AESI = adverse event of special interest; B-NHL = B-cell non-Hodgkin lymphoma; DLBCL = diffuse large B-cell lymphoma; ICANS = immune effector cell-associated neurotoxicity syndrome; ICE = immune effector cell-associated encephalopathy assessment tool; iNHL = indolent B-cell non-Hodgkin lymphoma; LBCL = large B-cell lymphoma; MCL = mantle cell lymphoma; SD = standard deviation.

Note: Safety Pool 01 includes GCT3013-01. Safety Pool 01+04 includes GCT3013-01 and GCT3013-04. All B-NHL is composed of the LBCL population plus subjects with iNHL (n=128) and MCL (n=38) from the escalation and expansion parts of the trials.

Note: ICANS events are graded according to (Lee et al 2019).

[a] Percentage calculated based on subjects with at least 1 ICANS event.

[b] Based on longest recorded CRS duration in subjects with >1 ICANS event.

Data cutoff date:31 Jan 2022

Clinical tumor lysis syndrome (CTLS)

Grading for CTLS severity was according to the Cairo-Bishop defined criteria (Coiffier et al., 2008). A diagnosis of TLS required that 2 or more of the following metabolic abnormalities occurred within 3 days before or up to 7 days after the initiation of therapy: hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia. CTLS was present when laboratory TLS was accompanied by an increased creatinine level, seizures, cardiac dysrhythmia, or death.

A total of 5 subjects in Safety Pool 01+04 experienced CTLS. Three subjects with LBCL experienced CTLS: 2 from GCT3013-01 aNHL (LBCL) Expansion Part (both DLBCL) and 1 from GCT3013-04 Escalation Part (HGBCL). In all subjects the events were grade 3 or 4. Two subjects from the iNHL/MCL Expansion Part also were assessed with CTLS and in both subjects the events were grade 1 or 2.

Safety Pool 01: GCT3013-01 (ESC + EXP)

In the Safety Pool 01 LBCL group (N=167), 3 (1.8%) subjects experienced the TEAE of TLS and in all 3 subjects the TEAEs were considered treatment-related. In 2 (1.2%) subjects, the events met the criteria for CTLS and in both subjects the CTLS was grade 3 or higher. Both events of CTLS occurred in setting of disease progression and were unresolved at time of subject death.

Safety Pool 01+04: GCT3013-01 (ESC + EXP) + GCT3013-04 (ESC + EXP)

In the Safety Pool 01+04 All B-NHL group (N=374), 7 (1.9%) subjects experienced the TEAE of tumor lysis syndrome and in 6 (1.6%) subjects the TEAEs were considered treatment-related. In 5 (1.3%) subjects, the events met the criteria for CTLS and in 3 (0.8%) subjects the CTLS was grade 3 or higher.

AESIs in the updated safety analyses (DCO 30 June 2022):

In the primary safety pool 01 (LBCL), no major changes were seen in the AESIs of CRS, ICANS or CTLS between the initial safety analysis and the update. This is in line with the observations in the initial safety analysis that these AESIs mainly tend to occur during the first cycles of epcoritamab treatment. In the supportive safety pool 01 + 04 (All B-NHL), two new grade 4-5 CRS events and two new grade 4-5 ICANS events were reported following the first full dose of epcoritamab. However, these high-grade events occurred in subjects with very aggressive forms of MCL i.e., patients outside of the intended target population of the current application.

Other safety topics identified by the applicant

Neurological events

Treatment-emergent neurological events were analysed using 2 approaches. Neurological events were analysed by the definition provided in Topp et al, 2015. In addition, neurological events were also assessed using a broad definition that included all TEAEs classified as SOC of nervous system disorders or psychiatric disorders, excluding high-level group terms of sleep disorders and disturbances, and peripheral neuropathies. ICANS is included as one of the PTs in both searches and is discussed separately as an AESI.

Safety Pool 01: GCT3013-01 (ESC + EXP)

In the Safety Pool 01 LBCL group (N=167) using the Topp et al, 2015 definition, 43 (25.7%) subjects experienced at least 1 neurological event, and 17 (10.2%) subjects had neurological events considered related to epcoritamab by the investigator (Table 64). PTs reported in ≥2% subjects included ICANS (6.0%; 10 subjects), dizziness (5.4%; 9 subjects), paresthesia (3.6%; 6 subjects), and tremor (3.6%; 6 subjects). All neurological events using the Topp definition were grade 1 or 2 in severity except for the following, reported for 1 subject each: ICANS (grade 5), loss of consciousness (grade 5), facial paralysis (grade 3), and delirium (grade 3). Of note, except for the ICANS event, all grade 3 or higher events were considered unrelated to epcoritamab by the investigator. Most of the neurological events using the Topp et al, 2015 definition occurred in the first 2 cycles of treatment (Week ≤8).

Using the broad definition for neurological events, 59 (35.3%) subjects had neurological events and 24 (14.4%) subjects had neurological events considered related to epcoritamab by the investigator (Table 65). PTs reported in ≥2% subjects included 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 neurological events using the broad definition occurred in the first 2 cycles of treatment (Week ≤8).

Safety Pool 01+04: GCT3013-01 (ESC + EXP) + GCT3013-04 (ESC + EXP)

In the Safety Pool 01+04 All B-NHL group (N=374) using the Topp et al, 2015 definition**,** 102 (27.3%) subjects experienced at least 1 neurological event, and 48 (12.8%) subjects had neurological events considered related to epcoritamab by the investigator (Table 64). PTs reported in ≥2% subjects included dizziness (6.4%; 24 subjects), ICANS (6.1%; 23 subjects), paresthesia (3.2%; 12 subjects), and tremor (2.4%; 9 subjects). All neurological events using the Topp definition were grade 1 or 2 in severity except for grade 3 syncope in 2 subjects and the following reported for 1 subject each: ICANS (grade 5), consciousness (grade 5), facial paralysis (grade 3), loss of depressed level of consciousness

(grade 3), dizziness (grade 3), Bell's palsy (grade 3), and delirium (grade 3). Of note, except for ICANS, all grade 3 or higher events were considered unrelated to epcoritamab by the investigator. Most of the neurological events using the (Topp et al, 2015) definition occurred in the first 2 cycles of treatment (Week ≤8).

Using the broad definition for neurological events, 141 (37.7%) subjects had neurological events and 62 (16.6%) subjects had neurological events considered related to epcoritamab by the investigator (Table 65). PTs reported in ≥2% subjects included headache (12.6%; 47 subjects), dizziness (6.4%; 24 subjects), ICANS (6.1%; 23 subjects), paresthesia (3.2%; 12 subjects), and tremor (2.4%; 9 subjects). Most of the neurological events using the broad definition occurred in the first 2 cycles of treatment (Week ≤8).

Table 51: Summary of Neurological Events Using the Topp Definition Reported for More Than 1 Subject by SOC and PT (48 mg Safety Analysis Set – Escalation + Expansion)

System Organ Class Preferred Term, n (%)	Safety Pool 01				Safety Pool 01+04					
	LBCL (N=167)		DLBCL (N=148)		LBCL (N=208)		DLBCL (N=188)		All B-NHL (N=374)	
	All	Related	All	Related	All	Related	All	Related	All	Related
Subjects with ≥1 neurological event by Topp method	**43 (25.7%)**	**17 (10.2%)**	**40 (27.0%)**	**16 (10.8%)**	**51 (24.5%)**	**20 (9.6%)**	**47 (25.0%)**	**19 (10.1%)**	**102 (27.3%)**	**48 (12.8%)**
Nervous system disorders	**40 (24.0%)**	**16 (9.6%)**	**37 (25.0%)**	**15 (10.1%)**	**47 (22.6%)**	**19 (9.1%)**	**43 (22.9%)**	**18 (9.6%)**	**91 (24.3%)**	**45 (12.0%)**
ICANS	10 (6.0%)	10 (6.0%)	9 (6.1%)	9 (6.1%)	11 (5.3%)	11 (5.3%)	10 (5.3%)	10 (5.3%)	23 (6.1%)	23 (6.1%)
Dizziness	9 (5.4%)	0	8 (5.4%)	0	9 (4.3%)	0	8 (4.3%)	0	24 (6.4%)	7 (1.9%)
Paraesthesia	6 (3.6%)	1 (0.6%)	6 (4.1%)	1 (0.7%)	6 (2.9%)	1 (0.5%)	6 (3.2%)	1 (0.5%)	12 (3.2%)	4 (1.1%)
Tremor	6 (3.6%)	2 (1.2%)	6 (4.1%)	2 (1.4%)	6 (2.9%)	2 (1.0%)	6 (3.2%)	2 (1.1%)	9 (2.4%)	5 (1.3%)
Hypo-aesthesia	3 (1.8%)	0	3 (2.0%)	0	4 (1.9%)	0	4 (2.1%)	0	6 (1.6%)	1 (0.3%)
Lethargy	3 (1.8%)	2 (1.2%)	3 (2.0%)	2 (1.4%)	3 (1.4%)	2 (1.0%)	3 (1.6%)	2 (1.1%)	6 (1.6%)	3 (0.8%)
Dysgeusia	1 (0.6%)	0	1 (0.7%)	0	2 (1.0%)	1 (0.5%)	2 (1.1%)	1 (0.5%)	3 (0.8%)	1 (0.3%)
Memory impairment	2 (1.2%)	1 (0.6%)	2 (1.4%)	1 (0.7%)	2 (1.0%)	1 (0.5%)	2 (1.1%)	1 (0.5%)	3 (0.8%)	1 (0.3%)
Syncope	2 (1.2%)	1 (0.6%)	1 (0.7%)	1 (0.7%)	2 (1.0%)	1 (0.5%)	1 (0.5%)	1 (0.5%)	4 (1.1%)	1 (0.3%)
Neuralgia	1 (0.6%)	1 (0.6%)	1 (0.7%)	1 (0.7%)	1 (0.5%)	1 (0.5%)	1 (0.5%)	1 (0.5%)	2 (0.5%)	2 (0.5%)
Post herpetic neuralgia	0	0	0	0	1 (0.5%)	0	1 (0.5%)	0	3 (0.8%)	0
Somno-lence	0	0	0	0	1 (0.5%)	0	1 (0.5%)	0	2 (0.5%)	0
Psychiatric disorders	**5 (3.0%)**	**1 (0.6%)**	**5 (3.4%)**	**1 (0.7%)**	**7 (3.4%)**	**1 (0.5%)**	**7 (3.7%)**	**1 (0.5%)**	**17 (4.5%)**	**4 (1.1%)**
Mental status	3 (1.8%)	1 (0.6%)	3 (2.0%)	1 (0.7%)	3 (1.4%)	1 (0.5%)	3 (1.6%)	1 (0.5%)	4 (1.1%)	1 (0.3%)

changes										
Delirium	1 (0.6%)	0	1 (0.7%)	0	2 (1.0%)	0	2 (1.1%)	0	3 (0.8%)	0
Confu-sional state	1 (0.6%)	0	1 (0.7%)	0	1 (0.5%)	0	1 (0.5%)	0	6 (1.6%)	2 (0.5%)
Halluci-nation	0	0	0	0	1 (0.5%)	0	1 (0.5%)	0	4 (1.1%)	1 (0.3%)

Abbreviations: B-NHL = B-cell non-Hodgkin lymphoma; DLBCL = diffuse large B-cell lymphoma; ICANS = immune effector cell-associated neurotoxicity syndrome; iNHL = indolent B-cell non-Hodgkin lymphoma; LBCL = large B-cell lymphoma; MCL = mantle cell lymphoma; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SOC = system organ class.

Note: Safety Pool 01 includes GCT3013-01. Safety Pool 01+04 includes GCT3013-01 and GCT3013-04. All B-NHL is composed of the LBCL population plus subjects with iNHL (n=128) and MCL (n=38) from the escalation and expansion parts of the trials. Percentages calculated based on N. Sorted by descending frequency in the Safety Pool 01+04 LBCL All column.

Note: Adverse events are classified using MedDRA v24.1 and are counted only once per system organ class and only once per preferred term. More than 1 PT could be reported per subject.

Note: Include neurological toxicity events defined by Topp (Topp et al, 2015).

Data cutoff date:31 Jan 2022

Source: Table 5.7

Table 52: Summary of Neurological Events Using the Broad Definition Reported in More Than 1 Subject by SOC and PT (48 mg Safety Analysis Set – Escalation + Expansion)

System Organ Class Preferred Term, n (%)	Safety Pool 01				Safety Pool 01+04					
	LBCL (N=167)		DLBCL (N=148)		LBCL (N=208)		DLBCL (N=188)		All B-NHL (N=374)	
	All	Related	All	Related	All	Related	All	Related	All	Related
Subjects with ≥1 neurological event by broad definition	**59 (35.3%)**	**24 (14.4%)**	**53 (35.8%)**	**20 (13.5%)**	**71 (34.1%)**	**27 (13.0%)**	**64 (34.0%)**	**23 (12.2%)**	**141 (37.7%)**	**62 (16.6%)**
Nervous system disorders	**52 (31.1%)**	**23 (13.8%)**	**46 (31.1%)**	**19 (12.8%)**	**62 (29.8%)**	**26 (12.5%)**	**55 (29.3%)**	**22 (11.7%)**	**121 (32.4%)**	**57 (15.2%)**
Head-ache	21 (12.6%)	9 (5.4%)	17 (11.5%)	6 (4.1%)	24 (11.5%)	9 (4.3%)	20 (10.6%)	6 (3.2%)	47 (12.6%)	18 (4.8%)
ICANS	10 (6.0%)	10 (6.0%)	9 (6.1%)	9 (6.1%)	11 (5.3%)	11 (5.3%)	10 (5.3%)	10 (5.3%)	23 (6.1%)	23 (6.1%)
Dizziness	9 (5.4%)	0	8 (5.4%)	0	9 (4.3%)	0	8 (4.3%)	0	24 (6.4%)	7 (1.9%)
Paraesthesia	6 (3.6%)	1 (0.6%)	6 (4.1%)	1 (0.7%)	6 (2.9%)	1 (0.5%)	6 (3.2%)	1 (0.5%)	12 (3.2%)	4 (1.1%)
Tremor	6 (3.6%)	2 (1.2%)	6 (4.1%)	2 (1.4%)	6 (2.9%)	2 (1.0%)	6 (3.2%)	2 (1.1%)	9 (2.4%)	5 (1.3%)
Hypo-aesthesia	3 (1.8%)	0	3 (2.0%)	0	4 (1.9%)	0	4 (2.1%)	0	6 (1.6%)	1 (0.3%)
Lethargy	3 (1.8%)	2 (1.2%)	3 (2.0%)	2 (1.4%)	3 (1.4%)	2 (1.0%)	3 (1.6%)	2 (1.1%)	6 (1.6%)	3 (0.8%)
Dys-geusia	1 (0.6%)	0	1 (0.7%)	0	2 (1.0%)	1 (0.5%)	2 (1.1%)	1 (0.5%)	3 (0.8%)	1 (0.3%)
Memory impairment	2 (1.2%)	1 (0.6%)	2 (1.4%)	1 (0.7%)	2 (1.0%)	1 (0.5%)	2 (1.1%)	1 (0.5%)	3 (0.8%)	1 (0.3%)
Syncope	2 (1.2%)	1 (0.6%)	1 (0.7%)	1 (0.7%)	2 (1.0%)	1 (0.5%)	1 (0.5%)	1 (0.5%)	4 (1.1%)	1 (0.3%)

System Organ Class Preferred Term, n (%)	Safety Pool 01				Safety Pool 01+04					
	LBCL (N=167)		DLBCL (N=148)		LBCL (N=208)		DLBCL (N=188)		All B-NHL (N=374)	
	All	Related	All	Related	All	Related	All	Related	All	Related
Neuralgia	1 (0.6%)	1 (0.6%)	1 (0.7%)	1 (0.7%)	1 (0.5%)	1 (0.5%)	1 (0.5%)	1 (0.5%)	2 (0.5%)	2 (0.5%)
Post herpetic neuralgia	0	0	0	0	1 (0.5%)	0	1 (0.5%)	0	3 (0.8%)	0
Sciatica	1 (0.6%)	0	1 (0.7%)	0	1 (0.5%)	0	1 (0.5%)	0	2 (0.5%)	0
Somnolence	0	0	0	0	1 (0.5%)	0	1 (0.5%)	0	2 (0.5%)	0
Transient ischaemic attack	1 (0.6%)	0	1 (0.7%)	0	1 (0.5%)	0	1 (0.5%)	0	2 (0.5%)	0
Psychiatric disorders	**12 (7.2%)**	**1 (0.6%)**	**12 (8.1%)**	**1 (0.7%)**	**15 (7.2%)**	**1 (0.5%)**	**15 (8.0%)**	**1 (0.5%)**	**35 (9.4%)**	**7 (1.9%)**
Anxiety	4 (2.4%)	0	4 (2.7%)	0	5 (2.4%)	0	5 (2.7%)	0	6 (1.6%)	0
Mental status changes	3 (1.8%)	1 (0.6%)	3 (2.0%)	1 (0.7%)	3 (1.4%)	1 (0.5%)	3 (1.6%)	1 (0.5%)	4 (1.1%)	1 (0.3%)
Agitation	1 (0.6%)	0	1 (0.7%)	0	2 (1.0%)	0	2 (1.1%)	0	6 (1.6%)	1 (0.3%)
Delirium	1 (0.6%)	0	1 (0.7%)	0	2 (1.0%)	0	2 (1.1%)	0	3 (0.8%)	0
Depression	2 (1.2%)	0	2 (1.4%)	0	2 (1.0%)	0	2 (1.1%)	0	5 (1.3%)	1 (0.3%)
Confusional state	1 (0.6%)	0	1 (0.7%)	0	1 (0.5%)	0	1 (0.5%)	0	6 (1.6%)	2 (0.5%)
Emotional distress	1 (0.6%)	0	1 (0.7%)	0	1 (0.5%)	0	1 (0.5%)	0	2 (0.5%)	0
Hallucination	0	0	0	0	1 (0.5%)	0	1 (0.5%)	0	4 (1.1%)	1 (0.3%)
Irritability	0	0	0	0	0	0	0	0	2 (0.5%)	0

Abbreviations: B-NHL = B-cell non-Hodgkin lymphoma; DLBCL = diffuse large B-cell lymphoma; ICANS = immune effector cell-associated neurotoxicity syndrome; iNHL = indolent B-cell non-Hodgkin lymphoma; LBCL = large B-cell lymphoma; MCL = mantle cell lymphoma; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SOC = system organ class.

Note: Safety Pool 01 includes GCT3013-01. Safety Pool 01+04 includes GCT3013-01 and GCT3013-04. All B-NHL is composed of the LBCL population plus subjects with iNHL (n=128) and MCL (n=38) from the escalation and expansion parts of the trials. Percentages calculated based on N. Sorted by descending frequency in the Safety Pool 01+04 LBCL All column.

Note: Adverse events are classified using MedDRA v24.1 and are counted only once per system organ class and only once per preferred term.

Note: Method of determining events: SOC of nervous system disorders or psychiatric disorders excluding high-level group terms of sleep disorders and disturbances, and peripheral neuropathies.

Data cutoff date:31 Jan 2022

Source: Table 5.6

Cytopenia events

Cytopenia events are based on grouped terms of neutropenia (PTs of neutropenia and neutrophil count decreased), febrile neutropenia (same PT), thrombocytopenia (SMQ of hematopoietic

thrombocytopenia narrow search), and anemia (PTs of anemia, red blood cell count decreased, hemoglobin decreased, serum ferritin decreased, and hematocrit decreased).

Safety Pool 01: GCT3013-01 (ESC + EXP)

In the Safety Pool 01 LBCL group (N=167), a total of 47 (28.1%) subjects had ≥1 neutropenia event (grouped term), and 36 of the 47 subjects had ≥1 grade 3 or 4 neutropenia event (Table 66).

- Treatment with G-CSF was administered in 25 (15.0%) subjects. The neutropenia events resolved in all but 3 of these 25 subjects in the GCT3013-01 aNHL pivotal expansion cohort as of the data cutoff. These 3 subjects were continuing on treatment in C11 or later and managing ongoing neutropenia with filgrastim.
- Seven (4.2%) subjects in the GCT3013-01 aNHL pivotal expansion cohort experienced epcoritamab dose delays due to events of neutropenia. Five of the subjects received concomitant treatment for the event while 2 of the subjects had only the dose delays. The neutropenia events resolved in all 7 subjects.

Febrile neutropenia was experienced by 4 (2.4%) subjects: the maximum severity was grade 3 in 3 (1.8%) subjects and grade 4 in 1 (0.6%) subject (Table 66). The febrile neutropenia resolved in all 4 subjects following treatment with G-CSF.

The incidence of neutropenia events (grouped term + febrile neutropenia) was >10% through the Week 12 to ≤36 period (15.6%, 12.5%, 18.3%, and 7.5% of subjects during the Week ≤8, Week 8 to ≤12,Week 12 to ≤36, and Week 36+ time periods, respectively), while the incidences for thrombocytopenia events (grouped term) (13.8%, 0%, 2.9%, and 0%, respectively) and anemia events (grouped term) (18.0%, 0.8%, 4.8%, and 0%, respectively) decreased after the Week ≤8 period with no events reported after Week 36 as of the data cutoff for anemia and thrombocytopenia.

Safety Pool 01+04: GCT3013-01 (ESC + EXP) + GCT3013-04 (ESC + EXP)

In the Safety Pool 01+04 All B-NHL group (N=374), a total of 106 (28.3%) subjects had ≥1 neutropenia event, and 88 of the 106 subjects had ≥1 grade 3 or 4 neutropenia event (Table 66). Treatment with G-CSF was administered to 69 (18.4%) subjects. No subjects in Safety Pools 01 and 01+04 discontinued treatment due to a TEAE of any cytopenia.

Table 53: Summary of Neutropenia Events (48 mg Safety Analysis Set – Escalation + Expansion)

Number of subjects, n(%)	Safety Pool 01		Safety Pool 01+04		
	LBCL (N=167)	DLBCL (N=148)	LBCL (N=208)	DLBCL (N=188)	All B-NHL (N=374)
Subjects with ≥1 neutropenia (grouped term) [a]	**47 (28.1%)**	**42 (28.4%)**	**63 (30.3%)**	**58 (30.9%)**	**106 (28.3%)**
Grade 1	5 (3.0%)	5 (3.4%)	5 (2.4%)	5 (2.7%)	6 (1.6%)
Grade 2	6 (3.6%)	5 (3.4%)	6 (2.9%)	5 (2.7%)	12 (3.2%)
Grade 3	19 (11.4%)	17 (11.5%)	28 (13.5%)	26 (13.8%)	43 (11.5%)
Grade 4	17 (10.2%)	15 (10.1%)	24 (11.5%)	22 (11.7%)	45 (12.0%)
Grade 5	0	0	0	0	0
Number of episodes per subject [b]					
1 event	31 (66.0%)	28 (66.7%)	37 (58.7%)	34 (58.6%)	62 (58.5%)
2 events	7 (14.9%)	5 (11.9%)	9 (14.3%)	7 (12.1%)	18 (17.0%)
3 events	5 (10.6%)	5 (11.9%)	8 (12.7%)	8 (13.8%)	15 (14.2%)
≥4 events	4 (8.5%)	4 (9.5%)	9 (14.3%)	9 (15.5%)	11 (10.4%)
Subjects with G-CSF treatment required	25 (15.0%)	22 (14.9%)	37 (17.8%)	34 (18.1%)	69 (18.4%)

Number of subjects, n(%)	Safety Pool 01		Safety Pool 01+04		
	LBCL (N=167)	DLBCL (N=148)	LBCL (N=208)	DLBCL (N=188)	All B-NHL (N=374)
Subjects with ≥1 event of febrile neutropenia	**4 (2.4%)**	**4 (2.7%)**	**5 (2.4%)**	**5 (2.7%)**	**7 (1.9%)**
Grade 1	0	0	0	0	0
Grade 2	0	0	0	0	0
Grade 3	3 (1.8%)	3 (2.0%)	4 (1.9%)	4 (2.1%)	6 (1.6%)
Grade 4	1 (0.6%)	1 (0.7%)	1 (0.5%)	1 (0.5%)	1 (0.3%)
Grade 5	0	0	0	0	0
Subjects with G-CSF treatment required	4 (2.4%)	4 (2.7%)	5 (2.4%)	5 (2.7%)	6 (1.6%)

Abbreviations: B-NHL = B-cell non-Hodgkin lymphoma; DLBCL = diffuse large B-cell lymphoma; G-CSF = granulocyte-colony stimulating factor; iNHL = indolent B-cell non-Hodgkin lymphoma; LBCL = large B-cell lymphoma; MCL = mantle cell lymphoma; PT = preferred term.

Note: Safety Pool 01 includes GCT3013-01. Safety Pool 01+04 includes GCT3013-01 and GCT3013-04. All B-NHL is composed of the LBCL population plus subjects with iNHL (n=128) and MCL (n=38) from the escalation and expansion parts of the trials.

[a] Includes PTs of neutropenia and neutrophil counts decreased.

[b] Percentage calculated based on number of subjects with at least 1 event in the analysis.

Data cutoff date:31 Jan 2022

Source: Table 5.13

Regarding decreased numbers of platelets, the applicant reported the number of events of major bleeding related to the occurrence of ≥Grade 3 thrombocytopaenia. There were 7 (1.9%) patients with major bleeding events, assessed using the EMA/CHMP definition, among those patients who had on-treatment Grade ≥3 thrombocytopenia (platelet count < 50 $x10^9$/L). The events were retroperitoneal haemorrhage, upper gastrointestinal haemorrhage and hypovolemic shock, small intestinal haemorrhage, lip haemorrhage, diarrhoea haemorrhagic, gastrointestinal haemorrhage, and mouth haemorrhage. All patients had a relevant medical history such as thrombocytopenia, anemia, chronic kidney disease, and gastrointestinal haemorrhage. None of the major bleeding events were fatal and none were considered related to epcoritamab. Of the 7 patients, 2 had a dose delay related to the major bleeding event. All 7 of the major bleeding events outcomes were reported as resolved.

Infections

Safety Pool 01: GCT3013-01 (ESC + EXP)

In the Safety Pool 01 LBCL group (N=167), 77 (46.1%) subjects experienced at least 1 TEAE in the Infections and infestations SOC; the TEAEs were considered related to epcoritamab by the investigator in 14 (8.4%) subjects, and were grade 3 or 4 in severity for 24 (14.4%) subjects (Table 67). Serious TEAEs that coded to the Infections and infestations SOC were reported in 27 (16.2%) subjects and fatal TEAEs in 4 (2.4%) subjects; none of the fatal TEAEs were considered related to epcoritamab by the investigator. TEAEs that led to treatment discontinuation were reported for 5 (3.0%) subjects and TEAEs that led to dose delay were reported in 22 (13.2%) subjects. Details within each category are provided below.

The incidence of Infection was 26.9% of 167 subjects during the Week ≤8 period, 6.7% of 120 subjects during the Week 8 to ≤12 period, 28.8% of 104 subjects during the Week 12 to ≤36 period, and 28.3% of 53 subjects during the Week 36+ period. The incidences of Infections were similar during the Week ≤8 period, Week 12 to ≤36 period, and Week 36+ period; the latter periods were longer in duration, but epcoritamab dosing was less frequent.

In the Safety Pool 01 LBCL group:

- Infections reported for ≥2% of subjects included UTI and pneumonia in 9 (5.4%) subjects each; COVID-19 in 8 (4.8%) subjects; oral candidiasis and upper respiratory tract infection in 6 (3.6%) subjects each; and sepsis and cellulitis in 4 (2.4% each) subjects.
    - Infections considered treatment-related by the investigator reported for ≥1% of subjects included oral candidiasis in 3 (1.8%) subjects; and upper respiratory tract infection and oral herpes in 2 (1.2%) subjects.
- Grade 3 or 4 infections reported for 2 or more subjects included COVID-19 and sepsis in 4 (2.4%) subjects each; pneumonia and cellulitis in 3 (1.8%) subjects each; and COVID-19 pneumonia, septic shock, and upper respiratory tract infection in 2 (1.2%) subjects each.
    - Treatment-related grade 3 or 4 infections as assessed by the investigator included sepsis and upper respiratory tract infection in 1 (0.6%) subject each.
    a. Serious TEAEs of Infection reported for 2 or more subjects included pneumonia and sepsis in 4 (2.4%) subjects; COVID-19, COVID-19 pneumonia, and cellulitis in 3 (1.8%) subjects each; and bacteremia, septic shock, and upper respiratory tract infection in 2 (1.2%) subjects each.
        a. Serious TEAEs of Infection considered epcoritamab-related by the investigator included sepsis, upper respiratory tract infection, and oral herpes in 1 (0.6%) subject each.
    b. Fatal TEAEs in the Infections and infestations SOC included COVID-19 in 2 (1.2%) subjects, COVID-19 pneumonia in 1 (0.6%) subject, and PML in 1 (0.6%) subject with onset of PML reported as D13, presumed to be related to prior treatment with rituximab. None of these fatal TEAEs was considered related to epcoritamab by the investigator. More specifically on the case of PML, this concerned a 50-60-year-old male with stage III DLBCL who received the priming dose of epcoritamab 0.16 mg on C1D1 and the intermediate dose of epcoritamab 0.8 mg on C1D8, which was the last epcoritamab dose administered. On Day 13, the patient experienced Grade 2 PML. On Day 15, a magnetic resonance imaging scan showed progressive multifocal white matter abnormality suggest of PML. On Day 16, lumbar puncture showed presence of John Cunningham (JC) virus (level was not quantifiable). The event of PML worsened to Grade 5 on Day 137. Lymphocytes were consistently low prior to the start of treatment with epcoritamab on Day 1 through the end of treatment visit on Day 23. Rituximab was part of every treatment regimen prior to enrolment in the study, including the most recent in combination with lenalidomide, which was stopped 64 days prior to starting epcoritamab. Additionally, the subject received HSCT on Days -721 to -641 as well as bendamustine on Days -278 to -193.

Safety Pool 01+04: GCT3013-01 (ESC + EXP) + GCT3013-04 (ESC + EXP)

In the Safety Pool 01+04 All B-NHL group (N=374), 174 (46.5%) subjects experienced at least 1 TEAE in the Infections and infestations SOC; the TEAEs were considered related to epcoritamab by the investigator in 43 (11.5%) subjects and were grade 3 or 4 in severity in 62 (16.6%) subjects (Table 67). Serious TEAEs in the Infections and infestations SOC were reported in 70 (18.7%) subjects and fatal TEAEs in 9 (2.4%) subjects; none of the fatal TEAEs were considered related to epcoritamab by the investigator. TEAEs that led to treatment discontinuation were reported in 9 (2.4%) subjects and to dose delay in 63 (16.8%) subjects. Details within each category are provided below.

The incidence of Infection was 27.8% of 374 subjects during the Week ≤8 period, 13.1% of 275 subjects during the Week 8 to ≤12 period, 29.4% of 235 subjects during the Week 12 to ≤36 period, and 30.4% of 92 subjects during the Week 36+ period. The incidences of Infections were similar during the Week ≤8 period, Week 12 to ≤36 period, and Week 36+ period; the latter periods were longer in duration, but epcoritamab dosing was less frequent.

In the Safety Pool 01+04 All B-NHL group:

- Grade 3 or 4 infections reported for ≥1% or more subjects included COVID-19 and pneumonia in 7 (1.9%) subjects; UTI in 6 (1.6%) subjects; sepsis in 5 (1.3%) subjects; and COVID-19 pneumonia and herpes zoster in 4 (1.1%) subjects each.
    - Treatment-related grade 3 or 4 infections as assessed by the investigator included pneumonia, sepsis, and herpes zoster in 2 (0.5%) subjects each; and upper respiratory tract infection, anorectal infection, cytomegalovirus infection, bronchitis, UTI, cytomegalovirus infection reactivation, infectious pleural effusion, and pneumocystis jirovecii pneumonia in 1 (0.3%) subject each.
- Serious TEAEs of Infection reported for >1% subjects included pneumonia in 9 (2.4%) subjects; COVID-19 and COVID-19 pneumonia in 7 (1.9%) subjects each; sepsis and herpes zoster in 5 (1.3%) subjects each; and septic shock in 4 (1.1%) subjects.
    - Serious TEAEs of Infection considered related to epcoritamab by the investigator included pneumonia in 3 (0.8%) subjects; sepsis and herpes zoster in 2 (0.5%) subjects each; and COVID-19, upper respiratory tract infection, UTI, anorectal infection, bronchitis, oral herpes, cytomegalovirus infection reactivation, infectious pleural effusion, and pneumocystis jirovecii pneumonia in 1 (0.3%) subject each.
- Fatal TEAEs in the Infections and infestations SOC included COVID-19 pneumonia in 2 (0.5%) subjects; COVID-19 in 2 (0.5%) subjects; and PML, necrotizing fasciitis, pneumonia, pneumonia aspiration, and septic shock in 1 (0.3%) subject each. No fatal infections were considered related to epcoritamab by the investigator. Concurrent cytopaenia was defined within 14 days prior to the infection event onset through the date of patient's deaths. Of the 9 patients, 6 experienced concurrent neutropenia or leukopenia (5 patients Grade 3-4) and 6 patients had concurrent lymphopenia (5 subjects Grade 3-4). Overall, of the 9 patients with a fatal infection, 8 had concurrent cytopaenias, in which 7 were Grade 3-4.

Table 54: Infections: Overview of Treatment-Emergent Adverse Events in the System Organ Class Infections and Infestations (48 mg Safety Analysis Set – Escalation + Expansion)

	Safety Pool 01		Safety Pool 01+04		
TEAEs in the System Organ Class Infections and Infestations, n (%)	**LBCL (N=167)**	**DLBCL (N=148)**	**LBCL (N=208)**	**DLBCL (N=188)**	**All B-NHL (N=374)**
Number of Subjects with ≥1:					
TEAE	77 (46.1%)	67 (45.3%)	94 (45.2%)	84 (44.7%)	174 (46.5%)
Related TEAE	14 (8.4%)	13 (8.8%)	24 (11.5%)	23 (12.2%)	43 (11.5%)
Grade 3 or 4 TEAE	24 (14.4%)	21 (14.2%)	31 (14.9%)	28 (14.9%)	62 (16.6%)
Grade 3 or 4 related TEAE	2 (1.2%)	2 (1.4%)	7 (3.4%)	7 (3.7%)	13 (3.5%)
TEAE by worst toxicity grade					
1	12 (7.2%)	12 (8.1%)	14 (6.7%)	14 (7.4%)	25 (6.7%)
2	37 (22.2%)	30 (20.3%)	45 (21.6%)	38 (20.2%)	81 (21.7%)
3	22 (13.2%)	19 (12.8%)	29 (13.9%)	26 (13.8%)	56 (15.0%)
4	2 (1.2%)	2 (1.4%)	2 (1.0%)	2 (1.1%)	3 (0.8%)
5	4 (2.4%)	4 (2.7%)	4 (1.9%)	4 (2.1%)	9 (2.4%)
Serious TEAE	27 (16.2%)	24 (16.2%)	33 (15.9%)	30 (16.0%)	70 (18.7%)
Serious Related TEAE	2 (1.2%)	2 (1.4%)	7 (3.4%)	7 (3.7%)	15 (4.0%)
TEAE leading to treatment discontinuation	5 (3.0%)	5 (3.4%)	5 (2.4%)	5 (2.7%)	9 (2.4%)
TEAE leading to dose delay	22 (13.2%)	20 (13.5%)	28 (13.5%)	26 (13.8%)	63 (16.8%)
Fatal TEAE	4 (2.4%)	4 (2.7%)	4 (1.9%)	4 (2.1%)	9 (2.4%)
Fatal related TEAE	0	0	0	0	0

Abbreviations: B-NHL = B-cell non-Hodgkin lymphoma; CTCAE = Common Terminology Criteria for Adverse Events; DLBCL = diffuse large B-cell lymphoma; iNHL = indolent B-cell non-Hodgkin lymphoma; LBCL = large B-cell lymphoma; MCL = mantle cell lymphoma; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.
Note: Safety Pool 01 includes GCT3013-01. Safety Pool 01+04 includes GCT3013-01 and GCT3013-04. All B-NHL is composed

of the LBCL population plus subjects with iNHL (n=128) and MCL (n=38) from the escalation and expansion parts of the trials. Percentages calculated based on N.
Note: Adverse events are classified using MedDRA v24.1 and CTCAE v5.0, and are counted only once per category.
Data cutoff date:31 Jan 2022
Source: Table 3.3 (TEAEs), Table 3.11 (gr 3 or 4 TEAEs), Table 3.6 (by grade), Table 3.9 (dose delay), Table 3.10 (treatment discontinuation), Table 3.12 (fatal), Table 3.13 (serious TEAEs)

As the occurrence of the SOC Infections and infestations was not restricted to the first 8 weeks of treatment, the applicant was requested to provide an updated analysis of serious infections. As shown in Table ***68***, the incidence of infections increased from the DCO date of 31 Jan 2022 to 30 June 2022.

Table 55: Infections: Overview of TEAEs in the System Organ Class Infections and Infestatons (48 mg Safety Analysis Set – Escalation + Expansion

TEAEs in the System Organ Class Infections and Infestations, n (%)	Safety Pool 01 LBCL		Safety Pool 01+04 All B-NHL	
	Initial (N=167)	Update (N=167)	Initial (N=374)	Update (N=431)
Number of Subjects With ≥1:				
TEAE	77 (46.1%)	89 (53.3%)	174 (46.5%)	238 (55.2%)
Related TEAE	14 (8.4%)	19 (11.4%)	43 (11.5%)	62 (14.4%)
Grade 3 or 4 TEAE	24 (14.4%)	36 (21.6%)	62 (16.6%)	96 (22.3%)
Grade 3 or 4 related TEAE	2 (1.2%)	4 (2.4%)	13 (3.5%)	18 (4.2%)
TEAE by Worst Toxicity Grade				
1	12 (7.2%)	11 (6.6%)	25 (6.7%)	32 (7.4%)
2	37 (22.2%)	37 (22.2%)	81 (21.7%)	99 (23.0%)
3	22 (13.2%)	31 (18.6%)	56 (15.0%)	84 (19.5%)
4	2 (1.2%)	3 (1.8%)	3 (0.8%)	4 (0.9%)
5	4 (2.4%)	7 (4.2%)	9 (2.4%)	19 (4.4%)
Serious TEAE	27 (16.2%)	41 (24.6%)	70 (18.7%)	114 (26.5%)
Serious related TEAE	2 (1.2%)	5 (3.0%)	15 (4.0%)	20 (4.6%)
TEAE leading to treatment discontinuation	5 (3.0%)	10 (6.0%)	9 (2.4%)	23 (5.3%)
TEAE leading to dose delay	22 (13.2%)	37 (22.2%)	63 (16.8%)	106 (24.6%)
Fatal TEAE	4 (2.4%)	7 (4.2%)	9 (2.4%)	19 (4.4%)
Fatal related TEAE	0	0	0	0

The most common PTs (>1% of subjects) in the primary safety pool 01 were COVID-19, COVID-19 pneumonia, pneumonia, sepsis, cellulitis, upper respiratory tract infection, bacteraemia, progressive multifocal leukoencephalopathy and septic shock. COVID-19, COVID-19 pneumonia and pneumonia accounted for most new infections reported from the initial DCO date to the updated analysis. A majority of the fatal TEAEs of infection were also associated with COVID-19 (6/7 fatal cases).

In the primary safety pool 01, the incidence of Infection was

- 28.1% during the Week ≤8 period,
- 6.7% during the >Week 8 to ≤12 period,
- 20.2% during the >Week 12 to ≤24 period,
- 20.3% during the >Week 24 to ≤36 period, and
- 55.7% during the >Week 36+ period.

An increased number and rate of Infections were observed in the >Week 36+ period in this safety update compared to the same period in the original SCS (i.e., 34/61 subjects [55.7%] versus 15/53 subjects [28.3%], respectively). Most of the increase in the >Week 36+ period was due to COVID-19,

which occurred in 4/53 subjects (7.5%) in the original analysis versus 18/61 subjects (29.5%) in this update.

The updated data on infections in the supportive safety pool were similar to that observed for the primary safety pool.

Injection-related reactions

Safety Pool 01: GCT3013-01 (ESC + EXP)

In the Safety Pool 01 LBCL group (N=167), 50 (29.9%) subjects experienced at least 1 TEAE of injection site reaction (Table 69). 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. Median time to first injection site reaction was 22.5 days (range: 1, 255) and median time to resolution was 11.5 days (range: 1, 252). PTs for injection site reactions reported in ≥1% of subjects included injection site reaction (22.2%); injection site erythema (8.4%); injection site pain and injection site pruritus (2.4% each); and injection site hypertrophy, injection site inflammation, and injection site rash (1.2% each). The incidence of injection site reactions was highest during the Week ≤8 period (26.9%) and was 19.2% during the Week 8 to ≤12 period, 15.4% during the Week 12 to ≤36 period, and 5.7% during the Week 36+ period.

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. The injection site reactions were reported as resolved in all but 1 subject who had grade 1 events on C1D16 (right side) and C1D23 (left side), was started on oral loratadine 10 mg, and who continued epcoritamab treatment and was in C11 of treatment as of the data cutoff date.

Safety Pool 01+04: GCT3013-01 (ESC + EXP) + GCT3013-04 (ESC + EXP)

In the Safety Pool 01+04 All B-NHL group (N=374), 150 (40.1%) subjects experienced at least 1 TEAE of injection site reaction (Table 69). In all subjects, the maximum grade event was either grade 1 (34.0%; 127 subjects) or grade 2 (6.1%; 23 subjects). No grade 3 or higher events were observed. Median time to first injection site reaction was 16.0 days (range: 1, 255) and median time to resolution was 15.0 days (range: 1, 345). Forty-eight (12.8%) subjects required treatment. PTs for injection site reactions reported in ≥1% of subjects included injection site reaction (31.0%), injection site erythema (9.1%), injection site rash (2.7%), injection site pruritus (1.9%), injection site pain (1.6%), and injection site inflammation (1.1%). The incidence of injection site reactions was highest during the Week ≤8 period (36.9%) and was 22.9% during the Week 8 to ≤12 period, 20.9% during the Week 12 to ≤36 period, and 13.0% during the Week 36+ period.

Table 56: Summary of Injection Site Reaction Events (48 mg Safety Analysis Set – Escalation + Expansion)

	Safety Pool 01		Safety Pool 01+04		
	LBCL (N=167)	DLBCL (N=148)	LBCL (N=208)	DLBCL (N=188)	All B-NHL (N=374)
Subjects with ≥1 injection site reaction, n (%)	**50 (29.9%)**	**47 (31.8%)**	**78 (37.5%)**	**75 (39.9%)**	**150 (40.1%)**
Grade 1	47 (28.1%)	44 (29.7%)	73 (35.1%)	70 (37.2%)	127 (34.0%)
Grade 2	3 (1.8%)	3 (2.0%)	5 (2.4%)	5 (2.7%)	23 (6.1%)
Grade 3	0	0	0	0	0

Number of episodes per subject[a], n (%)					
1 event	22 (44.0%)	20 (42.6%)	33 (42.3%)	31 (41.3%)	68 (45.3%)
2 events	8 (16.0%)	7 (14.9%)	12 (15.4%)	11 (14.7%)	19 (12.7%)
3 events	5 (10.0%)	5 (10.6%)	6 (7.7%)	6 (8.0%)	15 (10.0%)
4 events	3 (6.0%)	3 (6.4%)	3 (3.8%)	3 (4.0%)	7 (4.7%)
≥5 events	12 (24.0%)	12 (25.5%)	24 (30.8%)	24 (32.0%)	41 (27.3%)
Subjects with ≥1 injection site reaction with treatment required, n (%)	**11 (6.6%)**	**11 (7.4%)**	**16 (7.7%)**	**16 (8.5%)**	**48 (12.8%)**
Time to first injection site reaction onset (days)					
n	50	47	78	75	150
Mean (SD)	28.5 (37.68)	28.1 (38.17)	22.4 (33.70)	21.9 (33.81)	23.1 (31.95)
Median	22.5	22.0	15.5	15.0	16.0
Minimum, Maximum	1, 255	1, 255	1, 255	1, 255	1, 255
Time to resolution of injection site reaction (days)					
Subjects with resolved event[a], n (%)	48 (96.0%)	45 (95.7%)	73 (93.6%)	70 (93.3%)	135 (90.0%)
Mean (SD)[b]	28.6 (49.79)	29.9 (51.14)	31.7 (56.80)	32.7 (57.80)	26.9 (44.13)
Median	11.5	12.0	15.0	15.0	15.0
Minimum, Maximum	1, 252	1, 252	1, 345	1, 345	1, 345

Abbreviations: B-NHL = B-cell non-Hodgkin lymphoma; DLBCL = diffuse large B-cell lymphoma; iNHL = indolent B-cell non-Hodgkin lymphoma; LBCL = large B-cell lymphoma; MCL = mantle cell lymphoma; SD = standard deviation.

Multiple injection site reaction events with overlapping or adjacent event intervals will be collapsed into single event, and the collapsed event will start from the earliest onset and end with the latest resolution time among overlapped events.

Include all treatment-emergent adverse events with high level term of injection site reactions.

Note: Safety Pool 01 includes GCT3013-01. Safety Pool 01+04 includes GCT3013-01 and GCT3013-04. All B-NHL is composed of the LBCL population plus subjects with iNHL (n=128) and MCL (n=38) from the escalation and expansion parts of the trials.

[a] Percentage calculated based on subjects with at least 1 injection site reaction event.

[b] Based on longest duration recorded injection site reaction in subjects with multiple collapsed events.

Data cutoff date:31 Jan 2022

Source: Table 5.11

Upon request, the applicant provided additional data on events of tumour flare and COVID-19.

Tumour flare

In the epcoritamab safety pools, a total of 7 aEs with the PT tumour flare were observed, leading to an overall rate of 1.9% (7/374). Six of the events were reported in the GCT3013-01 study and one in the GCT3013-04 study. No reports had a fatal outcome; 6 events of tumour flare were non serious and 1 was serious due to concurrent CRS and small intestinal haemorrhage requiring hospitalization. The median time to onset of tumour flare from study drug initiation was 16 days (range 5-34 days) and the median duration of tumour flare was 22.5 days (range 1-54 days). The maximum severity of all 7 events of tumour flare was Grade 2, there were no reports of concomitant intubation and/or airway obstruction, and all events were resolving or resolved.

COVID-19

A total of 40 patients experienced 54 events (40 serious, 14 nonserious) of COVID-19. Of the 54 events, 44 were Grade $\geq$3. Of the 54 events, 40 were serious and 4 were considered related to epcoritamab. Of the 54 events of COVID-19, event outcomes were resolved/resolving (n=32), not resolved (n=10), and fatal (n=12).

There were 13 patients who experienced at least 1 event of Grade >3 COVID-19 after epcoritamab was reintroduced, i.e. after a dose delay. In these 13 patients, 5 had no additional events of COVID-19 and 8 had subsequent events of COVID-19. There was a total of 9 subsequent events following epcoritamab reintroduction (one patient experienced a total of 3 COVID-19 events) of which 5 were serious and 4 were nonserious. Of the 9 recurrent COVID-19 events, 7 resolved and 2 did not resolve at the time of data cut-off. None of the subsequent COVID-19 events had a fatal outcome and 1 was considered related to epcoritamab. Subsequent COVID-19 events occurred from 14 to 93 days after resolution of the prior episode of COVID-19.

2.6.8.3. Serious adverse event/deaths/other significant events

Serious adverse events

Safety Pool 01: GCT3013-01 (ESC + EXP)

In the Safety Pool 01 LBCL group (N=167), 97 (58.1%) subjects experienced at least 1 serious TEAE and 61 (36.5%) subjects experienced at least 1 serious TEAE considered related to epcoritamab by the investigator (Table 70). Most serious TEAEs occurred early in treatment (Week ≤8).

- Serious TEAEs reported in ≥2% of subjects included CRS (31.1%); pleural effusion (4.8%); febrile neutropenia, ICANS, pneumonia, pyrexia, and sepsis (2.4% each).
- Treatment-related serious TEAEs reported in ≥1% of subjects were CRS (31.1%), ICANS (2.4%), and tumour pain (1.2%).

Safety Pool 01+04: GCT3013-01 (ESC + EXP) + GCT3013-04 (ESC + EXP)

In the Safety Pool 01+04 All B-NHL group (N=374), 218 (58.3%) subjects experienced at least 1 serious TEAE and 151 (40.4%) subjects experienced at least 1 SAE considered related to epcoritamab by the investigator (Table 70).

- Serious TEAEs reported in ≥2% of subjects included CRS (35.0%); pleural effusion (2.9%); pyrexia (2.7%); and ICANS and pneumonia (2.4% each).
- Treatment-related serious TEAEs reported in ≥1% of subjects were CRS (35.0%) and ICANS (2.4%).

Table 57: Serious TEAEs Reported in ≥2% of Subjects in Any Group by SOC and PT (48 mg Safety Analysis Set – Escalation + Expansion)

System Organ Class	Safety Pool 01				Safety Pool 01+04					
	LBCL (N=167)		DLBCL (N=148)		LBCL (N=208)		DLBCL (N=188)		All B-NHL (N=374)	
Preferred Term, n (%)	All	Related	All	Related	All	Related	All	Related	All	Related
Subjects with ≥1 Serious TEAE	**97 (58.1%)**	**61 (36.5%)**	**87 (58.8%)**	**54 (36.5%)**	**113 (54.3%)**	**74 (35.6%)**	**102 (54.3%)**	**66 (35.1%)**	**218 (58.3%)**	**151 (40.4%)**
Immune system disorders	**52 (31.1%)**	**52 (31.1%)**	**45 (30.4%)**	**45 (30.4%)**	**60 (28.8%)**	**60 (28.8%)**	**52 (27.7%)**	**52 (27.7%)**	**131 (35.0%)**	**131 (35.0%)**
Cytokine release syndrome	52 (31.1%)	52 (31.1%)	45 (30.4%)	45 (30.4%)	60 (28.8%)	60 (28.8%)	52 (27.7%)	52 (27.7%)	131 (35.0%)	131 (35.0%)
Infections and infestations	**27 (16.2%)**	**2 (1.2%)**	**24 (16.2%)**	**2 (1.4%)**	**33 (15.9%)**	**7 (3.4%)**	**30 (16.0%)**	**7 (3.7%)**	**70 (18.7%)**	**15 (4.0%)**

System Organ Class Preferred Term, n (%)	Safety Pool 01				Safety Pool 01+04					
	LBCL (N=167)		DLBCL (N=148)		LBCL (N=208)		DLBCL (N=188)		All B-NHL (N=374)	
	All	Related	All	Related	All	Related	All	Related	All	Related
Pneumonia	4 (2.4%)	0	4 (2.7%)	0	5 (2.4%)	1 (0.5%)	5 (2.7%)	1 (0.5%)	9 (2.4%)	3 (0.8%)
Sepsis	4 (2.4%)	1 (0.6%)	4 (2.7%)	1 (0.7%)	4 (1.9%)	1 (0.5%)	4 (2.1%)	1 (0.5%)	5 (1.3%)	2 (0.5%)
COVID-19	3 (1.8%)	0	3 (2.0%)	0	3 (1.4%)	0	3 (1.6%)	0	7 (1.9%)	1 (0.3%)
Nervous system disorders	**11 (6.6%)**	**5 (3.0%)**	**11 (7.4%)**	**5 (3.4%)**	**13 (6.3%)**	**6 (2.9%)**	**12 (6.4%)**	**6 (3.2%)**	**23 (6.1%)**	**13 (3.5%)**
ICANS	4 (2.4%)	4 (2.4%)	4 (2.7%)	4 (2.7%)	5 (2.4%)	5 (2.4%)	5 (2.7%)	5 (2.7%)	9 (2.4%)	9 (2.4%)
Respiratory, thoracic and mediastinal disorders	**12 (7.2%)**	**1 (0.6%)**	**9 (6.1%)**	**1 (0.7%)**	**12 (5.8%)**	**1 (0.5%)**	**9 (4.8%)**	**1 (0.5%)**	**20 (5.3%)**	**2 (0.5%)**
Pleural effusion	8 (4.8%)	1 (0.6%)	5 (3.4%)	1 (0.7%)	8 (3.8%)	1 (0.5%)	5 (2.7%)	1 (0.5%)	11 (2.9%)	2 (0.5%)
General disorders and administration site conditions	**9 (5.4%)**	**1 (0.6%)**	**9 (6.1%)**	**1 (0.7%)**	**9 (4.3%)**	**1 (0.5%)**	**9 (4.8%)**	**1 (0.5%)**	**19 (5.1%)**	**4 (1.1%)**
Pyrexia	4 (2.4%)	0	4 (2.7%)	0	4 (1.9%)	0	4 (2.1%)	0	10 (2.7%)	1 (0.3%)
Blood and lymphatic system disorders	**8 (4.8%)**	**3 (1.8%)**	**8 (5.4%)**	**3 (2.0%)**	**8 (3.8%)**	**3 (1.4%)**	**8 (4.3%)**	**3 (1.6%)**	**11 (2.9%)**	**3 (0.8%)**
Febrile neutropenia	4 (2.4%)	1 (0.6%)	4 (2.7%)	1 (0.7%)	4 (1.9%)	1 (0.5%)	4 (2.1%)	1 (0.5%)	5 (1.3%)	1 (0.3%)

Abbreviations: B-NHL = B-cell non-Hodgkin lymphoma; COVID-19 = coronavirus disease 2019; DLBCL = diffuse large B-cell lymphoma; ICANS = Immune effector cell-associated neurotoxicity syndrome; iNHL = indolent B-cell non-Hodgkin lymphoma; LBCL = large B-cell lymphoma; MCL = mantle cell lymphoma; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.

Note: Safety Pool 01 includes GCT3013-01. Safety Pool 01+04 includes GCT3013-01 and GCT3013-04. All B-NHL is composed of the LBCL population plus subjects with iNHL (n=128) and MCL (n=38) from the escalation and expansion parts of the trials. Percentages calculated based on N.

Note: Adverse events are classified using MedDRA v24.1 and are counted only once per system organ class and only once per preferred term.

Data cutoff date:31 Jan 2022

Source: Table 3.13

Fatal treatment-emergent adverse events and deaths

Fatal treatment-emergent adverse events

Safety Pool 01: GCT3013-01 (ESC + EXP)

In the Safety Pool 01 LBCL group (N=167), fatal TEAEs were reported for 12 (7.2%) subjects. COVID-19 and general physical health deterioration were reported for 2 (1.2%) subjects; all other fatal TEAEs were reported in 1 subject each. Nine of the deaths occurred during expansion and 3 of the deaths occurred during escalation.

Fatal treatment-emergent adverse events during expansion

All 9 of the fatal TEAEs were on-treatment events with onset during the first 2 cycles of treatment, except for the event of loss of consciousness, which occurred beyond the first 2 cycles (D119).

One fatal TEAE was considered related to epcoritamab by the investigator; this was an episode of **ICANS** in a 70-80-year-old female subject with DLBCL. Relevant medical history included hyperlipidemia (grade 1), type 2 diabetes mellitus (grade 2), hypertension (grade 1), and paresthesia (grade 1). Relevant medication history included pregabalin, insulin human injection, metformin/saxagliptin, pancreatin/simethicone/ ursodeoxycholic acid, sulfamethoxazole, and trimethoprim. A diagnosis of grade 3 pancreatitis was made on D10. ICANS was an on-treatment event with onset on Day 12, 5 days after the subject's second (and last) dose of epcoritamab (0.8 mg intermediate dose), and treatment with dexamethasone was initiated. An EEG showed non-convulsive status epilepticus, and antiepileptics were added. Brain MRI revealed multifocal cerebrovascular ischemia (grade 1, unrelated to epcoritamab). On D17, ICANS worsened to grade 4, and the subject developed hypertension, along with fever, diagnosed as grade 1 CRS, and tocilizumab was administered. Methylprednisolone and phenobarbital were also administered. On D18, the subject became comatose and was transferred to the ICU, where another dose of tocilizumab was administered. CRS was reported to resolve 4 days later and repeat CT scan showed possible improvement in pancreatitis but a new splenic infarction in the setting of platelet count decreased (grade 3). The subject's mental status continued to deteriorate, and she died on D25. Per Lugano, the subject had PD evaluated by the IRC (Days 6 to 24).

In addition, four of the fatal TEAEs were attributed to PD, two to COVID-19, and two to comorbidities/impact or prior therapies (progressive multifocal leukoencephalopahy attributed to prior treatment with rituximab, myocardial infarction attributed to prior history cardiovascular diseases). Brief narratives are provided in the clinical AR.

Table 58: Fatal TEAEs by SOC and PT (48 mg Safety Analysis Set – Escalation + Expansion)

System Organ Class Preferred Term, n (%)	Safety Pool 01				Safety Pool 01+04					
	LBCL (N=167)		DLBCL (N=148)		LBCL (N=208)		DLBCL (N=188)		All B-NHL (N=374)	
	All	Related	All	Related	All	Related	All	Related	All	Related
Subjects with ≥1 fatal TEAE	**12 (7.2%)**	**1 (0.6%)**	**11 (7.4%)**	**1 (0.7%)**	**12 (5.8%)**	**1 (0.5%)**	**11 (5.9%)**	**1 (0.5%)**	**19 (5.1%)**	**1 (0.3%)**
Infections and infestations	**4 (2.4%)**	**0**	**4 (2.7%)**	**0**	**4 (1.9%)**	**0**	**4 (2.1%)**	**0**	**9 (2.4%)**	**0**
COVID-19	2 (1.2%)	0	2 (1.4%)	0	2 (1.0%)	0	2 (1.1%)	0	2 (0.5%)	0
COVID-19 pneumonia	1 (0.6%)	0	1 (0.7%)	0	1 (0.5%)	0	1 (0.5%)	0	2 (0.5%)	0
Progressive multifocal leuko-encephalopathy	1 (0.6%)	0	1 (0.7%)	0	1 (0.5%)	0	1 (0.5%)	0	1 (0.3%)	0
Necrotising fasciitis	0	0	0	0	0	0	0	0	1 (0.3%)	0
Pneumonia	0	0	0	0	0	0	0	0	1 (0.3%)	0
Pneumonia aspiration	0	0	0	0	0	0	0	0	1 (0.3%)	0
Septic shock	0	0	0	0	0	0	0	0	1 (0.3%)	0
General disorders and administration	**2 (1.2%)**	**0**	**2 (1.4%)**	**0**	**2 (1.0%)**	**0**	**2 (1.1%)**	**0**	**2 (0.5%)**	**0**

System Organ Class Preferred Term, n (%)	Safety Pool 01				Safety Pool 01+04					
	LBCL (N=167)		DLBCL (N=148)		LBCL (N=208)		DLBCL (N=188)		All B-NHL (N=374)	
	All	Related	All	Related	All	Related	All	Related	All	Related
site conditions										
General physical health deterioration	2 (1.2%)	0	2 (1.4%)	0	2 (1.0%)	0	2 (1.1%)	0	2 (0.5%)	0
Nervous system disorders	**2 (1.2%)**	**1 (0.6%)**	**2 (1.4%)**	**1 (0.7%)**	**2 (1.0%)**	**1 (0.5%)**	**2 (1.1%)**	**1 (0.5%)**	**2 (0.5%)**	**1 (0.3%)**
Immune effector cell-associated neurotoxicity syndrome	1 (0.6%)	1 (0.6%)	1 (0.7%)	1 (0.7%)	1 (0.5%)	1 (0.5%)	1 (0.5%)	1 (0.5%)	1 (0.3%)	1 (0.3%)
Loss of consciousness	1 (0.6%)	0	1 (0.7%)	0	1 (0.5%)	0	1 (0.5%)	0	1 (0.3%)	0
Cardiac disorders	**1 (0.6%)**	**0**	**1 (0.7%)**	**0**	**1 (0.5%)**	**0**	**1 (0.5%)**	**0**	**1 (0.3%)**	**0**
Myocardial infarction	1 (0.6%)	0	1 (0.7%)	0	1 (0.5%)	0	1 (0.5%)	0	1 (0.3%)	0
Hepatobiliary disorders	**1 (0.6%)**	**0**	**1 (0.7%)**	**0**	**1 (0.5%)**	**0**	**1 (0.5%)**	**0**	**1 (0.3%)**	**0**
Hepatotoxicity	1 (0.6%)	0	1 (0.7%)	0	1 (0.5%)	0	1 (0.5%)	0	1 (0.3%)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**1 (0.6%)**	**0**	**0**	**0**	**1 (0.5%)**	**0**	**0**	**0**	**2 (0.5%)**	**0**
Malignant neoplasm progression	1 (0.6%)	0	0	0	1 (0.5%)	0	0	0	1 (0.3%)	0
Lymphoma transformation	0	0	0	0	0	0	0	0	1 (0.3%)	0
Respiratory, thoracic and mediastinal disorders	**1 (0.6%)**	**0**	**1 (0.7%)**	**0**	**1 (0.5%)**	**0**	**1 (0.5%)**	**0**	**2 (0.5%)**	**0**
Pulmonary embolism	1 (0.6%)	0	1 (0.7%)	0	1 (0.5%)	0	1 (0.5%)	0	1 (0.3%)	0
Lung opacity	0	0	0	0	0	0	0	0	1 (0.3%)	0

Abbreviations: B-NHL = B-cell non-Hodgkin lymphoma; COVID-19 = coronavirus disease 2019; DLBCL = diffuse large B-cell lymphoma; iNHL = indolent B-cell non-Hodgkin lymphoma; LBCL = large B-cell lymphoma; MCL = mantle cell lymphoma; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SOC = system organ class; TEAE = treatment-emergent adverse event.

Note: Safety Pool 01 includes GCT3013-01. Safety Pool 01+04 includes GCT3013-01 and GCT3013-04. All B-NHL is composed of the LBCL population plus subjects with iNHL (n=128) and MCL (n=38) from the escalation and expansion parts of the trials. Percentages calculated based on N. Sorted by descending frequency in the Safety Pool 01+04 LBCL All column.

Note: Adverse events are classified using MedDRA v24.1 and are counted only once per system organ class and only once per preferred term.

Data cutoff date:31 Jan 2022

Source: Table 3.12

Fatal Treatment-Emergent Adverse Events During Escalation

Three subjects treated at the 48 mg dosing regimen during the Escalation Part of trial GCT3013-01 had fatal TEAEs. Two were attributed to disease progression and 1 was due to COVID-19 pneumonia. Brief narratives are provided in the clinical AR.

Safety Pool 01+04: GCT3013-01 (ESC + EXP) + GCT3013-04 (ESC + EXP)

In the Safety Pool 01+04 All B-NHL group (N=374), fatal TEAEs were reported for 19 (5.1%) subjects. No fatal TEAEs were reported in the GCT3013-04 trial. COVID-19, COVID-19 pneumonia, and general physical health deterioration, reported for 2 (0.5%) subjects, were the only fatal TEAEs reported for more than 1 subject. Twelve of the fatal TEAEs occurred in LBCL subjects and are discussed above; 7 additional fatal TEAEs occurred in the All B-NHL group, and none were considered related to epcoritamab treatment by the investigator (6 subjects from the GCT3013-01 iNHL expansion cohort and 1 subject from the GCT3013-01 MCL expansion cohort). The 7 fatal TEAEs were attributed to disease progression in one subject, COVID-19 in one subject, existing comorbidities/impact of prior therapies in three subjects (necrotizing fasciitis, lung opacity, pneumonia), or other reasons not captured by those terms in two subjects (septic shock, aspiration pneumonia). Brief narratives are provided in the clinical AR.

Deaths

Safety Pool 01: GCT3013-01 (ESC + EXP)

In the Safety Pool 01 LBCL group (N=167), a total of 68 (40.7%) subjects died during the trial: 37/167 (22.2%) subjects died within the treatment-emergent period (60 days from last dose or 28 days from last dose for GCT3013-01 Dose Escalation Part [uncensored for start of subsequent anti-lymphoma treatment]) and 31/167 (18.6%) subjects died during the follow-up period. Overall, most deaths were caused by disease progression (32.3%; 54 subjects). Seven (4.2%) subjects died due to adverse events: 5 deaths were on treatment (COVID-19 pneumonia, COVID-19, hepatoxicity, ICANS, myocardial infarction) and 2 deaths were during follow up (PML, COVID-19) (Table 72).

Safety Pool 01+04: GCT3013-01 (ESC + EXP) + GCT3013-04 (ESC + EXP)

In the Safety Pool 01+04 All B-NHL group (N=374), a total of 102 (27.3%) subjects died during the trials: 56/374 (15.0%) subjects died within the treatment-emergent period (60 days from last dose [uncensored for start of subsequent anti-lymphoma treatment]) and 46/374 (12.3%) subjects died during the follow-up period. Overall, most deaths were caused by disease progression (20.9%; 78 subjects). Fifteen (4.0%) subjects died due to adverse events: 13 deaths were on treatment (COVID-19 pneumonia in 2 subjects; and COVID-19, hepatoxicity, ICANS, myocardial infarction, pneumonia, lymphoma transformation, necrotizing fasciitis, sepsis, septic shock, lung opacity, and pneumonia aspiration in 1 subject each) and 2 deaths occurred during the follow-up period (PML, COVID-19). Out of the 8 patients with an "other" cause of death, 5 were related to an adverse event (4 infection, 1 transplant complication) and 3 were related to disease progression.

The percentage of subjects who died was lower in the Safety Pool 01+04 All B-NHL group (27.3%) compared to the LBCL groups from Safety Pools 01 and 01+04 (40.7% and 39.9%, respectively) (Table 72) due to the lower proportion of iNHL subjects who died during the study (12.4%; 13/105 subjects) as a result of less time on study overall (enrollment ongoing as of data cutoff) and less aggressive disease than LBCL.

Table 59: Summary of Deaths (48 mg Safety Analysis Set – Escalation + Expansion)

Number subjects (%)	Safety Pool 01		Safety Pool 01+04		
	LBCL (N=167)	DLBCL (N=148)	LBCL (N=208)	DLBCL (N=188)	All B-NHL (N=374)
Deaths	**68 (40.7%)**	**62 (41.9%)**	**83 (39.9%)**	**76 (40.4%)**	**102 (27.3%)**
Primary Cause of Death					
Disease Progression	54 (32.3%)	49 (33.1%)	69 (33.2%)	63 (33.5%)	78 (20.9%)
Adverse Event	7 (4.2%)	7 (4.7%)	7 (3.4%)	7 (3.7%)	15 (4.0%)
Other	6 (3.6%)	5 (3.4%)	6 (2.9%)	5 (2.7%)	8 (2.1%)
Unknown	1 (0.6%)	1 (0.7%)	1 (0.5%)	1 (0.5%)	1 (0.3%)
Deaths within 60 days of first dose	**24 (14.4%)**	**21 (14.2%)**	**27 (13.0%)**	**23 (12.2%)**	**34 (9.1%)**
Primary Cause of Death					
Disease Progression	19 (11.4%)	16 (10.8%)	22 (10.6%)	18 (9.6%)	25 (6.7%)
Adverse Event	5 (3.0%)	5 (3.4%)	5 (2.4%)	5 (2.7%)	8 (2.1%)
Other	0	0	0	0	1 (0.3%)
Unknown	0	0	0	0	0
Deaths within 60 days of last dose	**37 (22.2%)**	**33 (22.3%)**	**42 (20.2%)**	**37 (19.7%)**	**56 (15.0%)**
Primary Cause of Death					
Disease Progression	30 (18.0%)	26 (17.6%)	35 (16.8%)	30 (16.0%)	40 (10.7%)
Adverse Event	5 (3.0%)	5 (3.4%)	5 (2.4%)	5 (2.7%)	13 (3.5%)
Other	2 (1.2%)[a]	2 (1.4%)	2 (1.0%)	2 (1.1%)	3 (0.8%)
Unknown	0	0	0	0	0

Abbreviations: B-NHL = B-cell non-Hodgkin lymphoma; DLBCL = diffuse large B-cell lymphoma; iNHL = indolent B-cell non-Hodgkin lymphoma; LBC L= large B-cell lymphoma; MCL = mantle cell lymphoma; TEAE = treatment-emergent adverse event.

Note: Safety Pool 01 includes GCT3013-01. Safety Pool 01+04 includes GCT3013-01 and GCT3013-04. All B-NHL is composed of the LBCL population plus subjects with iNHL (n=128) and MCL (n=38) from the escalation and expansion parts of the trials. Percentages calculated based on N.

[a] Other (n=2) deaths were due to: PD; loss of consciousness due to cerebral hemorrhage (related to PD)

Data cutoff date:31 Jan 2022

2.6.8.4. Laboratory findings

Haematology and coagulation

Treatment-emergent grade 3 or higher laboratory abnormalities (i.e., grade worsened from baseline) for select hematology parameters (hemoglobin, ANC, lymphocytes, and platelets) are in Table 73. The most common hematologic abnormality across all analysis groups was lymphopenia followed by neutropenia, thrombocytopenia, and anemia. Cytopenias were managed through dose delay and/or treatment with G-CSF for neutropenia.

Abnormal elevations in lymphocyte counts to grade 3 were infrequently observed (<1% of subjects across groups).

Table 60: Summary of Hematology and Coagulation Laboratory Results– Worsened from Baseline to On-Treatment CTCAE Grade (48 mg Safety Analysis Set – Escalation + Expansion)

Number of Subjects, (%)	Safety Pool 01		Safety Pool 01+04		
CTCAE Grade	LBCL (N=167)	DLBCL (N=148)	LBCL (N=208)	DLBCL (N=188)	All B-NHL (N=374)
ANC (Hypo), N	**158**	**140**	**199**	**180**	**356**

Number of Subjects, (%)	Safety Pool 01		Safety Pool 01+04		
CTCAE Grade	LBCL (N=167)	DLBCL (N=148)	LBCL (N=208)	DLBCL (N=188)	All B-NHL (N=374)
All grades	77 (48.7%)	67 (47.9%)	105 (52.8%)	94 (52.2%)	178 (50.0%)
Grade 3	28 (17.7%)	24 (17.1%)	40 (20.1%)	36 (20.0%)	60 (16.9%)
Grade 4	21 (13.3%)	20 (14.3%)	29 (14.6%)	28 (15.6%)	50 (14.0%)
Platelets (Hypo), N	**163**	**145**	**204**	**185**	**362**
All grades	80 (49.1%)	71 (49.0%)	111 (54.4%)	101 (54.6%)	182 (50.3%)
Grade 3	10 (6.1%)	9 (6.2%)	18 (8.8%)	16 (8.6%)	30 (8.3%)
Grade 4	11 (6.7%)	10 (6.9%)	12 (5.9%)	11 (5.9%)	17 (4.7%)
Hemoglobin (Hypo), N	**163**	**145**	**204**	**185**	**362**
All grades	101 (62.0%)	89 (61.4%)	124 (60.8%)	111 (60.0%)	215 (59.4%)
Grade 3	21 (12.9%)	20 (13.8%)	30 (14.7%)	28 (15.1%)	46 (12.7%)
Grade 4	0	0	0	0	0
Lymphocytes (Hypo), N	**156**	**138**	**197**	**178**	**346**
All grades	136 (87.2%)	121 (87.7%)	172 (87.3%)	156 (87.6%)	303 (87.6%)
Grade 3	59 (37.8%)	53 (38.4%)	67 (34.0%)	61 (34.3%)	109 (31.5%)
Grade 4	63 (40.4%)	55 (39.9%)	89 (45.2%)	80 (44.9%)	164 (47.4%)
Lymphocytes (Hyper), N	**156**	**138**	**184**	**166**	**325**
All grades	10 (6.4%)	9 (6.5%)	13 (6.6%)	12 (6.7%)	21 (6.1%)
Grade 3	1 (0.6%)	0	1 (0.5%)	0	1 (0.3%)
Grade 4	0	0	0	0	0

Abbreviations: ANC = absolute neutrophil count; B-NHL = B-cell non-Hodgkin lymphoma; CTCAE = Common Terminology Criteria for Adverse Events; DLBCL = diffuse large B-cell lymphoma; iNHL = indolent B-cell non-Hodgkin lymphoma; LBCL = large B-cell lymphoma; MCL = mantle cell lymphoma.

Note: Safety Pool 01 includes GCT3013-01. Safety Pool 01+04 includes GCT3013-01 and GCT3013-04. All B-NHL is composed of the LBCL population plus subjects with iNHL (n=128) and MCL (n=38) from the escalation and expansion parts of the trials. Percentages calculated based on N.

Each subject counted only once for the worst grade observed post-baseline (regardless of the baseline status).

Data cutoff date:31 Jan 2022

Source: Table 6.1

There were no grade 4 INR or aPTT observed in all epcoritamab-treated subjects (Safety Pool 01+04). Grade 3 INR or aPTT were observed for ≤2% of subjects across groups.

Biochemistry

Treatment-emergent grade 3 or higher laboratory abnormalities (i.e., grade worsened from baseline) for LFTs and electrolytes are provided in Table 74.

Table 61: Summary of Biochemistry Laboratory Results – Worsened from Baseline to On-Treatment CTCAE Grade (48 mg Safety Analysis Set – Escalation + Expansion)

Number of Subjects (%)	Safety Pool 01		Safety Pool 01+04		
CTCAE Grade	LBCL (N=167)	DLBCL (N=148)	LBCL (N=208)	DLBCL (N=188)	All B-NHL (N=374)
Alanine Aminotransferase (Hyper), N	**162**	**144**	**203**	**184**	**361**
All grades	72 (44.4%)	62 (43.1%)	90 (44.3%)	80 (43.5%)	162 (44.9%)
Grade 3	8 (4.9%)	6 (4.2%)	10 (4.9%)	8 (4.3%)	21 (5.8%)
Grade 4	0	0	0	0	1 (0.3%)
Aspartate Transaminase (Hyper) , N	**161**	**143**	**202**	**183**	**360**
All grades	74 (46.0%)	65 (45.5%)	95 (47.0%)	85 (46.4%)	160 (44.4%)
Grade 3	6 (3.7%)	4 (2.8%)	7 (3.5%)	5 (2.7%)	12 (3.3%)
Grade 4	1 (0.6%)	1 (0.7%)	1 (0.5%)	1 (0.5%)	2 (0.6%)

Number of Subjects (%) CTCAE Grade	Safety Pool 01		Safety Pool 01+04		
	LBCL (N=167)	DLBCL (N=148)	LBCL (N=208)	DLBCL (N=188)	All B-NHL (N=374)
Alkaline Phosphatase (Hyper) , N	**162**	**144**	**203**	**184**	**361**
All grades	51 (31.5%)	45 (31.3%)	65 (32.0%)	58 (31.5%)	109 (30.2%)
Grade 3	2 (1.2%)	1 (0.7%)	3 (1.5%)	2 (1.1%)	3 (0.8%)
Grade 4	0	0	0	0	0
Total Bilirubin (Hyper) , N	**162**	**144**	**203**	**184**	**361**
All grades	22 (13.6%)	20 (13.9%)	27 (13.3%)	25 (13.6%)	73 (20.2%)
Grade 3	4 (2.5%)	3 (2.1%)	4 (2.0%)	3 (1.6%)	10 (2.8%)
Grade 4	1 (0.6%)	1 (0.7%)	1 (0.5%)	1 (0.5%)	1 (0.3%)
Albumin (Hypo), N	**161**	**143**	**202**	**183**	**360**
All grades	109 (67.7%)	96 (67.1%)	139 (68.8%)	125 (68.3%)	235 (65.3%)
Grade 3	3 (1.9%)	2 (1.4%)	5 (2.5%)	3 (1.6%)	7 (1.9%)
Grade 4	0	0	0	0	0
Calcium (hyper), N	**49**	**44**	**66**	**60**	**107**
All grades	9 (18.4%)	7 (15.9%)	13 (19.7%)	11 (18.3%)	16 (15.0%)
Grade 3	1 (2.0%)	1 (2.3%)	1 (1.5%)	1 (1.7%)	1 (0.9%)
Grade 4	0	0	0	0	0
Magnesium (Hyper) , N	**158**	**141**	**199**	**181**	**357**
All grades	18 (11.4%)	16 (11.3%)	28 (14.1%)	25 (13.8%)	43 (12.0%)
Grade 3	4 (2.5%)	3 (2.1%)	4 (2.0%)	3 (1.7%)	5 (1.4%)
Grade 4	0	0	0	0	0
Magnesium (Hypo) , N	**158**	**141**	**199**	**181**	**357**
All grades	49 (31.0%)	46 (32.6%)	61 (30.7%)	58 (32.0%)	94 (26.3%)
Grade 3	0	0	0	0	0
Grade 4	0	0	0	0	1 (0.3%)
Sodium (Hypo) , N	**162**	**144**	**203**	**184**	**361**
All grades	92 (56.8%)	82 (56.9%)	120 (59.1%)	109 (59.2%)	201 (55.7%)
Grade 3	4 (2.5%)	4 (2.8%)	5 (2.5%)	5 (2.7%)	7 (1.9%)
Grade 4	0	0	0	0	0
Creatinine (Hyper) , N	**162**	**144**	**203**	**184**	**360**
All grades	40 (24.7%)	32 (22.2%)	57 (28.1%)	48 (26.1%)	93 (25.8%)
Grade 3	6 (3.7%)	4 (2.8%)	7 (3.4%)	4 (2.2%)	8 (2.2%)
Grade 4	0	0	0	0	0
Potassium (Hyper) , N	**162**	**144**	**203**	**184**	**361**
All grades	37 (22.8%)	32 (22.2%)	53 (26.1%)	47 (25.5%)	83 (23.0%)
Grade 3	2 (1.2%)	1 (0.7%)	3 (1.5%)	1 (0.5%)	7 (1.9%)
Grade 4	1 (0.6%)	1 (0.7%)	1 (0.5%)	1 (0.5%)	1 (0.3%)
Potassium (Hypo) , N	**162**	**144**	**203**	**184**	**361**
All grades	55 (34.0%)	50 (34.7%)	71 (35.0%)	65 (35.3%)	107 (29.6%)
Grade 3	7 (4.3%)	7 (4.9%)	13 (6.4%)	13 (7.1%)	16 (4.4%)
Grade 4	1 (0.6%)	1 (0.7%)	1 (0.5%)	1 (0.5%)	2 (0.6%)

Abbreviations: B-NHL = B-cell non-Hodgkin lymphoma; CTCAE = Common Terminology Criteria for Adverse Events; DLBCL = diffuse large B-cell lymphoma; iNHL = indolent B-cell non-Hodgkin lymphoma; LBCL = large B-cell lymphoma; MCL = mantle cell lymphoma.

Note: Safety Pool 01 includes GCT3013-01. Safety Pool 01+04 includes GCT3013-01 and GCT3013-04. All B-NHL is composed of the LBCL population plus subjects with iNHL (n=128) and MCL (n=38) from the escalation and expansion parts of the trials. Percentages calculated based on N.

Each patient was counted only once for the worst grade observed post-baseline (regardless of the baseline status)

Drug-induced liver abnormalities

Drug-induced liver injury (Hy's Law criteria) was defined as: 1) AST/ALT >3×ULN; 2) total bilirubin >2×ULN; 3) absence of initial findings of cholestasis (i.e., absence of elevation of ALP to >2× ULN); and 4) no other reason can be found to explain the combination of increased ALT and total bilirubin, such as viral hepatitis, etc. All potential events of elevations in ALT, AST, and total bilirubin occurring within a concurrent 30-day period are summarized for Safety Pools 01 and 01+04 in Table 75. A total of 9 (2.4%) of 374 subjects in Safety Pool 01+04 had LFT elevations that met the first 2 laboratory criteria for potential drug-induced liver injury: not all elevations occurred on the same day. These 9 subjects included 5 subjects with LBCL (including 4 DLBCL subjects), 3 subjects with iNHL (2 with FL, 1 with MZL), and 1 subject with MCL. LFT elevations in the 9 subjects were in the context of CRS (5 subjects), disease progression (3 subjects), or cholangitis (1 subject). The cases are briefly described below.

In the Safety Pool 01 LBCL group (N=167), 5 (3.0%) subjects had AST/ALT >3×ULN and total bilirubin >2×ULN within 30 days of epcoritamab administration. Out of the 5 subjects, 4 (2.4%) subjects had LFT elevations within 1 day of epcoritamab administration. In 3 subjects, the LFT elevations occurred in the context of progressive disease and in all 3 ALP was also elevated >2x ULN, with reported causes of death being either disease progression (n=2) or hepatotoxicity due to disease progression (n=1). In the other 2 subjects, the LFT elevations were transient and resolved along with concurrent TEAEs of CRS (n=1 with increased ALPS but <2xULN) or liver injury (n=1, cholangitis including ALP elevations >2xULN). The hepatotoxicity and liver injury were not considered related to epcoritamab by the investigator. Both subjects continued treatment and were ongoing as of the data cutoff date.

In the Safety Pool 01+04 All B-NHL group (N=374), 9 (2.4%) subjects had AST/ALT >3×ULN and total bilirubin >2×ULN concurrent within a 30-day period, including 7 (1.9%) subjects with concurrent elevations on the same day. The 9 subjects with potential DILIs were from the GCT3013-01 trial: 5 subjects from the pivotal aNHL pivotal expansion cohort (described above), 3 subjects from the iNHL expansion cohort, and 1 subject from the MCL expansion cohort. All 3 iNHL subjects had transaminase elevations concurrent with events of CRS that resolved, and the subjects continued with epcoritamab treatment (2 were ongoing as of the data cutoff). In 2 of the 3 patients ALP was also elevated >2x ULN, in the other patient ALP remained in the normal range. The MCL subject had LFT elevations concurrent with progressive disease, CRS, ICANS, and CTLS. ALP was elevated >2x ULN. This subject ultimately died, and disease progression was reported as the primary cause of death.

Table 62: Abnormal On-treatment Hepatic Laboratory Results (48 mg Safety Analysis Set – Escalation + Expansion)

Hepatic Elevation, n (%)	Safety Pool 01		Safety Pool 01+04		
	LBCL (N=167)	DLBCL (N=148)	LBCL (N=208)	DLBCL (N=188)	All B-NHL (N=374)
ALT or AST > 3x ULN	24 (14.4%)	20 (13.5%)	32 (15.4%)	28 (14.9%)	55 (14.7%)
ALT or AST > 5x ULN	11 (6.6%)	9 (6.1%)	13 (6.3%)	11 (5.9%)	27 (7.2%)
ALT or AST > 10x ULN	6 (3.6%)	5 (3.4%)	7 (3.4%)	6 (3.2%)	11 (2.9%)
ALT or AST > 20x ULN	1 (0.6%)	1 (0.7%)	1 (0.5%)	1 (0.5%)	3 (0.8%)
Total Bilirubin > 2x ULN	6 (3.6%)	5 (3.4%)	6 (2.9%)	5 (2.7%)	17 (4.5%)
Concurrent (1 day) ALT or AST > 3x ULN and total bilirubin > 2x ULN	4 (2.4%)	3 (2.0%)	4 (1.9%)	3 (1.6%)	7 (1.9%)
Concurrent (30 days) ALT or AST > 3x ULN and total bilirubin > 2x ULN	5 (3.0%)	4 (2.7%)	5 (2.4%)	4 (2.1%)	9 (2.4%)
ALT or AST > 3x ULN and total bilirubin > 2x	5 (3.0%)	4 (2.7%)	5 (2.4%)	4 (2.1%)	9 (2.4%)

ULN					

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; B-NHL = B-cell non-Hodgkin lymphoma; DLBCL = diffuse large B-cell lymphoma; iNHL = indolent B-cell non-Hodgkin lymphoma; LBCL = large B-cell lymphoma; MCL = mantle cell lymphoma; ULN=upper limit of normal.

Note: Safety Pool 01 includes GCT3013-01. Safety Pool 01+04 includes GCT3013-01 and GCT3013-04. All B-NHL is composed of the LBCL population plus subjects with iNHL (n=128) and MCL (n=38) from the escalation and expansion parts of the trials. Percentages calculated based on N.

Data cutoff date:31 Jan 2022 <02APR2022; Data Cutoff: 31JAN2022; Date Generated: 08JUN2022 05:59>

Vital signs

Table 76 summarizes clinically notable vital sign abnormalities for the primary and supportive safety analysis pools following the criteria specified in the study SAPs. Incidences were generally similar between pools, except for low systolic blood pressure and elevated temperature, which were more common in the supportive safety pool. The differences for those vital sign abnormalities reflect the corresponding higher rates in the DLBCL EXP cohort of GCT3013-04. In both safety pools, the most frequent abnormality was elevated temperature (>38°C).

Table 63: Summary of Clinically Notable On-Treatment Vital Signs (48 mg Dose-Studies GCT3013-01 and GCT3013-04 Safety Analysis Set)

	GCT3013-01 ESC+EXP	GCT3013-01+GCT3013-04 ESC+EXP			
	R/R LBCL (N = 167)	R/R DLBCL (N = 148)	R/R LBCL (N = 208)	R/R DLBCL (N = 188)	ALL B-NHL (N = 374)
Vital Sign: Systolic Blood Pressure (mmHg)					
Overall On-Treatment Period[a]					
Number of treated subjects	167	148	208	188	374
Elevated (≥180 mmHg and an increase ≥20 mmHg from baseline)	4 (2.4%)	4 (2.7%)	4 (1.9%)	4 (2.1%)	9 (2.4%)
Below normal (≤90 mmHg and a decrease ≥20 mmHg from baseline)	33 (19.8%)	30 (20.3%)	54 (26.0%)	50 (26.6%)	91 (24.3%)
Vital Sign: Diastolic Blood Pressure (mmHg)					
Overall On-Treatment Period[a]					
Number of treated subjects	167	148	208	188	374
Elevated (≥105 mmHg and an increase ≥15 mmHg from baseline)	3 (1.8%)	3 (2.0%)	4 (1.9%)	4 (2.1%)	11 (2.9%)
Below normal (≤50 mmHg and a decrease ≥15 mmHg from baseline)	28 (16.8%)	26 (17.6%)	39 (18.8%)	36 (19.1%)	81 (21.7%)
Vital Sign: Weight (kg)					
Overall On-Treatment Period[a]					
Number of treated subjects	167	148	208	188	374
Elevated (increase from baseline of ≥10%)	14 (8.4%)	13 (8.8%)	19 (9.1%)	18 (9.6%)	23 (6.1%)
Below normal (decrease from baseline of ≥10%)	13 (7.8%)	11 (7.4%)	17 (8.2%)	15 (8.0%)	31 (8.3%)
Vital Sign: Heart Rate (beats/min)					
Overall On-Treatment Period[a]					
Number of treated subjects	167	148	208	188	374
Elevated (≥120 bpm with increase from baseline of ≥15 bpm)	37 (22.2%)	34 (23.0%)	49 (23.6%)	45 (23.9%)	83 (22.2%)
Below normal (≤50 bpm with decrease from baseline of ≥15 bpm)	4 (2.4%)	4 (2.7%)	5 (2.4%)	5 (2.7%)	11 (2.9%)
Vital Sign: Temperature (C)					
Overall On-Treatment Period[a]					
Number of treated subjects	167	148	208	188	373
Elevated (>38 C)	84 (50.3%)	74 (50.0%)	116 (55.8%)	105 (55.9%)	226 (60.6%)
Below normal (<35 C)	4 (2.4%)	3 (2.0%)	5 (2.4%)	4 (2.1%)	9 (2.4%)

	GCT3013-01 ESC+EXP	GCT3013-01+GCT3013-04 ESC+EXP			
	R/R LBCL (N = 167)	R/R DLBCL (N = 148)	R/R LBCL (N = 208)	R/R DLBCL (N = 188)	ALL B-NHL (N = 374)
Vital Sign: Oxygen Saturation (%)					
Overall On-Treatment Period[a]					
Number of treated subjects	167	148	208	188	374
Below normal (<92% oxygen saturation)	19 (11.4%)	18 (12.2%)	26 (12.5%)	24 (12.8%)	44 (11.8%)

B-NHL = B-cell non-Hodgkin lymphoma; DLBCL = diffuse large B-cell lymphoma; ESC = escalation phase; EXP = expansion phase; LBCL = large B-cell lymphoma; R/R = relapsed or refractory

a. Unscheduled visits during the on-treatment period are included.

Note: Percentages calculated based on number of treated subjects in the analysis period.

Snapshot date: 02APR2022; Data Cutoff: 31JAN2022.

Overall, few subjects (16 in the Safety Pool GCT3013-01+GCT3013-04 ESC+EXP All B-NHL group, of which 9 were in the Safety Pool GCT3013-01 ESC+EXP LBCL group) experienced vital sign AEs that led to epcoritamab dose modification (i.e., dose delay; Table 77). No major differences were observed between the Safety Pool GCT3013-01 ESC+EXP LBCL group and the Safety Pool GCT3013-01+GCT3013-04 ESC+EXP All B-NHL group.

Table 64: Treatment-Emergent Vital Sign Adverse Events Leading to Dose Modification by Abnormality and Preferred Term (48 mg Dose-Studies GCT3013-01 and GCT3013-04 Safety Analysis Set)

Vital Sign Abnormality Preferred Term	GCT3013-01 ESC+EXP		GCT3013-01+GCT3013-04 ESC+EXP		
	R/R LBCL (N = 167)	R/R DLBCL (N = 148)	R/R LBCL (N = 208)	R/R DLBCL (N = 188)	ALL B-NHL (N = 374)
Blood pressure decreased[a]	2 (1.2%)	1 (0.7%)	2 (1.0%)	1 (0.5%)	3 (0.8%)
Hypotension	2 (1.2%)	1 (0.7%)	2 (1.0%)	1 (0.5%)	3 (0.8%)
Blood pressure increased[b]	0	0	0	0	1 (0.3%)
Hypertension	0	0	0	0	1 (0.3%)
Body temperature decreased[c]	0	0	0	0	0
Body temperature increased[d]	5 (3.0%)	5 (3.4%)	5 (2.4%)	5 (2.7%)	10 (2.7%)
Pyrexia	5 (3.0%)	5 (3.4%)	5 (2.4%)	5 (2.7%)	10 (2.7%)
Heart rate decreased[e]	0	0	0	0	0
Heart rate increased[f]	2 (1.2%)	2 (1.4%)	2 (1.0%)	2 (1.1%)	2 (0.5%)
Tachycardia	2 (1.2%)	2 (1.4%)	2 (1.0%)	2 (1.1%)	2 (0.5%)
Oxygen saturation decreased[g]	0	0	0	0	0
Weight decreased[h]	0	0	0	0	0
Weight increased[i]	0	0	0	0	0

B-NHL = B-cell non-Hodgkin lymphoma; DLBCL = diffuse large B-cell lymphoma; ESC = escalation phase; EXP = expansion phase; LBCL = large B-cell lymphoma; R/R = relapsed or refractory

a. Search terms comprise blood pressure decreased, blood pressure diastolic decreased, blood pressure systolic decreased, diastolic hypotension, hypotension, and hypotension NOS.

b. Search terms comprise blood pressure increased, blood pressure diastolic increased, blood pressure systolic increased, diastolic hypertension, hypertension, hypertension NOS, hypertensive crisis, hypertensive emergency, malignant hypertension, malignant hypertension NOS, systolic hypertension.

c. Search terms comprise body temperature decreased and hypothermia.

d. Search terms comprise body temperature increased, pyrexia, and hyperthermia.

e. Search terms comprise heart rate decreased, bradyarrhythmia, bradycardia, bradycardia NOS, central bradycardia, maximum heart rate decreased, and sinus bradycardia.

f. Search terms comprise heart rate increased, atrial tachycardia, maximum heart rate increased, sinus tachycardia, supraventricular tachyarrhythmia, supraventricular tachycardia, tachyarrhythmia, tachycardia, tachycardia aggravated, tachycardia irregular, tachycardia NOS, tachycardia paroxysmal, tachycardia paroxysmal NOS, ventricular tachyarrhythmia, and ventricular tachycardia.

g. Search terms comprise oxygen saturation decreased, anoxia, cyanosis, dependence on oxygen therapy, dependence on respirator, endotracheal intubation, hypoxia, mechanical ventilation, oxygen therapy, and venous oxygen saturation decreased.

h. Search terms comprise weight decreased, body mass index decreased, abnormal loss of weight, and underweight.

i. Search terms comprise weight increased, body mass index increased, abnormal weight gain, and overweight.

Note: Percentages calculated based on N.

Note: Adverse events are classified using MedDRA v24.1 and are counted only once per vital sign abnormality and only once per preferred term. TEAEs with action taken of dose interruption or dose delay are included in the analysis.

Snapshot date: 02APR2022; Data Cutoff: 31JAN2022.

Source: Table q147_3

Using the same MedDRA search criteria, no isolated vital sign AEs led to discontinuation of epcoritamab treatment in either safety pool.

Electrocardiogram (ECG) assessment

A total of 369 treated subjects in the supportive safety analysis pool (GCT3013-01+GCT3013-04 ESC+EXP All B-NHL) had at least one on-treatment ECG. Of these 369 subjects, 252 (68.3%) had at least one ECG with an abnormal interpretation. The worst observed abnormal ECG was clinically significant for 14 subjects, not clinically significant for 200 subjects, and unclassified for 38 subjects.

A summary of electrocardiogram QT interval using Fridericia's correction for the primary and supportive safety analysis pools is provided in Table 78. Per protocol, all subjects were required to have a screening and baseline ECG. However, some sites only reported QTcB, but not the QTcF result. Those ECG readings with only QTcB were not converted to QTcF, leading to some subjects without QTcF results. A total of 236 treated subjects in the supportive safety analysis pool (GCT3013-01+GCT3013-04 ESC+EXP All B-NHL) had at least one on-treatment QTcF result. Of these 236 subjects, 39 (16.5%) experienced on-treatment QTcF >450 – 480 ms, 9 (3.8%) experienced on-treatment QTcF >480 – 500 ms, and 7 (3.0%) experienced on-treatment QTcF >500 ms. One of the patients with QTcF >500 ms on-treatment also had QTcF >500 ms at baseline.

Table 65: Summary of Electrocardiogram QT Interval using Fridericia's Correction (48 mg Dose-Studies GCT3013-01 and GCT3013-04 Safety Analysis Set)

	GCT3013-01 ESC+EXP		GCT3013-01+GCT3013-04 ESC+EXP		
	R/R LBCL (N=167)	R/R DLBCL (N=148)	R/R LBCL (N=208)	R/R DLBCL (N=188)	ALL B-NHL (N=374)
Baseline					
Number of subjects	84	77	124	116	215
≤ 450 ms	77 (91.7%)	70 (90.9%)	114 (91.9%)	106 (91.4%)	195 (90.7%)
>450 - 480 ms	6 (7.1%)	6 (7.8%)	9 (7.3%)	9 (7.8%)	18 (8.4%)
>480 - 500 ms	0	0	0	0	0
>500 ms	1 (1.2%)	1 (1.3%)	1 (0.8%)	1 (0.9%)	2 (0.9%)
Overall on-treatment period[a]					
Number of treated subjects	104	94	143	132	236
≤ 450 ms	75 (72.1%)	68 (72.3%)	109 (76.2%)	102 (77.3%)	181 (76.7%)
>450 - 480 ms	22 (21.2%)	19 (20.2%)	25 (17.5%)	21 (15.9%)	39 (16.5%)
>480 - 500 ms	4 (3.8%)	4 (4.3%)	6 (4.2%)	6 (4.5%)	9 (3.8%)
>500 ms	3 (2.9%)	3 (3.2%)	3 (2.1%)	3 (2.3%)	7 (3.0%)

B NHL = B cell non-Hodgkin lymphoma; DLBCL = diffuse large B cell lymphoma; ESC = escalation; EXP = expansion; LBCL = large B cell lymphoma; max = maximum; min = minimum; R/R = relapsed or refractory;

a. Based on worst on-treatment QTcF result. Unscheduled visits during the on-treatment period are included.

Note: Percentages for post-baseline visits are calculated based on number of treated subjects in the analysis period.

A total of 40 (10.7%) subjects experienced at least 1 TEAE in the Cardiac disorders SOC, of which 7 (1.9%) were considered related. The most common PTs (≥1% of subjects) were tachycardia (n=10, 2.7%), sinus tachycardia (n=7, 1.9%), atrial fibrillation (n=7, 1.9%), and cardiac failure (n=4, 1.1%). The PTs for the 7 related TEAEs in the Cardiac disorders SOC included tachycardia (n=2, 0.5%), sinus tachycardia (n=2, 0.5%), sinus bradycardia (n=1, 0.3%), cardiovascular disorder (n=1, 0.3%), and myocarditis (n=1, 0.3%). A total of 8 (2.1%) subjects experienced serious and Grade 3 or 4 TEAEs in the Cardiac disorders SOC, none of which were considered related to epcoritamab. None of the TEAEs in the Cardiac disorders SOC led to epcoritamab discontinuation.

2.6.8.5. In vitro biomarker test for patient selection for safety

N/A

2.6.8.6. Safety in special populations

Intrinsic factors

The focus for safety analysis in subgroups will be on the safety analysis pool 01+04 All B-NHL as this is the largest pool.

Age

Table 66: Overview of TEAEs by Age (48 mg Safety Analysis Set – Escalation + Expansion)

Number of Subjects, n (%)	Safety Pool 01+04								
	LBCL (N=208)			DLBCL (N=188)			All B-NHL (N=374)		
	<65 years (N=96)	65-<75 years (N=73)	≥75 years (N=39)	<65 years (N=80)	65-<75 years (N=69)	≥75 years (N=39)	<65 years (N=157)	65-<75 years (N=144)	≥75 years (N=73)
Number of Subjects with ≥1:									
TEAE	96 (100.0%)	72 (98.6%)	39 (100.0%)	80 (100.0%)	68 (98.6%)	39 (100.0%)	155 (98.7%)	140 (97.2%)	73 (100.0%)
Related TEAE	82 (85.4%)	63 (86.3%)	36 (92.3%)	69 (86.3%)	59 (85.5%)	36 (92.3%)	136 (86.6%)	126 (87.5%)	70 (95.9%)
Grade 3 and higher TEAE	69 (71.9%)	46 (63.0%)	26 (66.7%)	59 (73.8%)	44 (63.8%)	26 (66.7%)	106 (67.5%)	89 (61.8%)	53 (72.6%)
Grade 3 and higher related TEAE	38 (39.6%)	27 (37.0%)	14 (35.9%)	33 (41.3%)	26 (37.7%)	14 (35.9%)	60 (38.2%)	55 (38.2%)	30 (41.1%)
TEAE by worst toxicity grade									
1	11 (11.5%)	6 (8.2%)	4 (10.3%)	9 (11.3%)	6 (8.7%)	4 (10.3%)	15 (9.6%)	13 (9.0%)	6 (8.2%)
2	16 (16.7%)	20 (27.4%)	9 (23.1%)	12 (15.0%)	18 (26.1%)	9 (23.1%)	34 (21.7%)	38 (26.4%)	14 (19.2%)
3	32 (33.3%)	29 (39.7%)	18 (46.2%)	27 (33.8%)	28 (40.6%)	18 (46.2%)	55 (35.0%)	50 (34.7%)	39 (53.4%)
4	31 (32.3%)	12 (16.4%)	7 (17.9%)	27 (33.8%)	11 (15.9%)	7 (17.9%)	44 (28.0%)	31 (21.5%)	10 (13.7%)
5	6 (6.3%)	5 (6.8%)	1 (2.6%)	5 (6.3%)	5 (7.2%)	1 (2.6%)	7 (4.5%)	8 (5.6%)	4 (5.5%)
Serious TEAE	57 (59.4%)	34 (46.6%)	22 (56.4%)	49 (61.3%)	31 (44.9%)	22 (56.4%)	92 (58.6%)	78 (54.2%)	48 (65.8%)
Serious Related TEAE	38 (39.6%)	22 (30.1%)	14 (35.9%)	33 (41.3%)	19 (27.5%)	14 (35.9%)	65 (41.4%)	55 (38.2%)	31 (42.5%)
TEAE leading to treatment discontinuation	6 (6.3%)	5 (6.8%)	4 (10.3%)	5 (6.3%)	5 (7.2%)	4 (10.3%)	7 (4.5%)	9 (6.3%)	8 (11.0%)
TEAE leading to dose delay	38 (39.6%)	22 (30.1%)	16 (41.0%)	31 (38.8%)	20 (29.0%)	16 (41.0%)	68 (43.3%)	49 (34.0%)	34 (46.6%)
Fatal TEAE[a]	6 (6.3%)	5 (6.8%)	1 (2.6%)	5 (6.3%)	5 (7.2%)	1 (2.6%)	7 (4.5%)	8 (5.6%)	4 (5.5%)
Fatal related TEAE	0	1 (1.4%)	0	0	1 (1.4%)	0	0	1 (0.7%)	0
AESI									
CRS (All grade)	52 (54.2%)	48 (65.8%)	19 (48.7%)	44 (55.0%)	44 (63.8%)	19 (48.7%)	91 (58.0%)	96 (66.7%)	43 (58.9%)
Grade 3 and higher	5 (5.2%)	0	3 (7.7%)	5 (6.3%)	0	3 (7.7%)	9 (5.7%)	3 (2.1%)	4 (5.5%)
ICANS (All grade)	5 (5.2%)	3 (4.1%)	3 (7.7%)	4 (5.0%)	3 (4.3%)	3 (7.7%)	8 (5.1%)	10 (6.9%)	5 (6.8%)
Grade 3 and higher	0	1 (1.4%)	0	0	1 (1.4%)	0	0	1 (0.7%)	0
CTLS (All grade)	3 (3.1%)	0	0	2 (2.5%)	0	0	4 (2.5%)	1 (0.7%)	0
Grade 3 and higher	3 (3.1%)	0	0	2 (2.5%)	0	0	3 (1.9%)	0	0

There were no clinically meaningful differences in the frequency and severity of events across TEAE categories and the AESIs of CRS and ICANS between age groups. CTLS occurred only in subjects younger than 75 years of age, of which 4 out of 5 in the Safety Pool 01+04 All B-NHL population were < 65 years. However, the number of CTLS observations is too limited to draw any conclusions in terms of a potential association with age.

Table 67: Selected Treatment-Emergent Adverse Events by Age Group (48 mg Dose-Studies GCT3013-01 ESC+EXP R/R LBCL)

Analysis Set: GCT3013-01 ESC+EXP R/R LBCL	Age <65 (N = 83)	Age 65-74 (N = 53)	Age ≥75 (N = 31)
Total AEs	83 (100%)	52 (98.1%)	31 (100%)
Serious AEs – Total	51 (61.4%)	28 (52.8%)	18 (58.1%)
- Fatal	6 (7.2%)	5 (9.4%)	1 (3.2%)
- Hospitalization/prolong existing hospitalization	51 (61.4%)	26 (49.1%)	17 (54.8%)
- Life-threatening	5 (6.0%)	2 (3.8%)	2 (6.5%)
- Disability/incapacity	3 (3.6%)	2 (3.8%)	0
- Other (medically significant)	4 (4.8%)	3 (5.7%)	1 (3.2%)
AE leading to drop-out	6 (7.2%)	5 (9.4%)	2 (6.5%)
Psychiatric disorders	9 (10.8%)	16 (30.2%)	3 (9.7%)
Nervous system disorders	27 (32.5%)	17 (32.1%)	13 (41.9%)
Accidents and injuries	9 (10.8%)	3 (5.7%)	6 (19.4%)
Cardiac disorders	13 (15.7%)	11 (20.8%)	2 (6.5%)
Vascular disorders	14 (16.9%)	10 (18.9%)	3 (9.7%)
Cerebrovascular disorders	0	1 (1.9%)	0
Infections and infestations	42 (50.6%)	22 (41.5%)	13 (41.9%)
Anticholinergic syndrome	0	0	0
Quality of life decreased	0	0	0
Any postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	10 (12.0%)	6 (11.3%)	6 (19.4%)
Other AEs appearing more frequently in older patients:			
Asthenia	4 (4.8%)	6 (11.3%)	2 (6.5%)
Cough	3 (3.6%)	6 (11.3%)	4 (12.9%)
Cytokine release syndrome	39 (47.0%)	31 (58.5%)	14 (45.2%)
Diarrhoea	10 (12.0%)	11 (20.8%)	12 (38.7%)
Dizziness	3 (3.6%)	5 (9.4%)	1 (3.2%)
Dyspnoea	5 (6.0%)	4 (7.5%)	4 (12.9%)
Fatigue	20 (24.1%)	9 (17.0%)	12 (38.7%)
Injection site erythema	3 (3.6%)	7 (13.2%)	4 (12.9%)
Injection site reaction	11 (13.3%)	18 (34.0%)	8 (25.8%)
Insomnia	5 (6.0%)	10 (18.9%)	3 (9.7%)
Oedema peripheral	7 (8.4%)	5 (9.4%)	7 (22.6%)
Urinary tract infection	1 (1.2%)	3 (5.7%)	5 (16.1%)

ESC = escalation; EXP = expansion; LBCL = large B-cell lymphoma; R/R = relapsed or refractory

Note: Percentages calculated based on N. Adverse events are classified using MedDRA v24.1.
Snapshot date: 02APR2022; Data Cutoff: 31JAN2022.
Source: Table q155_1

Sex

In the Safety Pool 01+04 All B-NHL group (N=374), the proportion of females is lower than males. The incidence of CRS of any grade in females and males was 65.0% and 59.3%, respectively, and for serious TEAEs of CRS was 34.3% and 35.5%. These differences between females and males are smaller than that observed in the LBCL group with an incidence of CRS of 67.5% in females and 50.4% om males. In the LBCL group serious TEAEs of CRS were reported in 34.9% vs 24.8%. Cases of CRS in Safety Pool 01 All B-NHL subjects were grade of 3 or 4 severity for 4.2% and 4.3% of subjects, respectively. In the LBCL subgroup these numbers were 6.0% and 2.4%, respectively. CTLS only occurred in male subjects (5 [2.2%] subjects).

Race

In the Safety Pool 01+04 All B-NHL group (N=374), 55.3% of subjects were White, 29.7% were Asian, 3.2% were Other. In general, the frequency and severity of events were similar between race subgroups across TEAE categories and the AESIs of CTLS and ICANS. White subjects had a higher incidence of serious TEAEs compared to Asian subjects (65.7% vs 44.1%, respectively). Higher frequencies in any grade CRS were noted in the Asian subgroup (79.3%) compared to the White or Other subgroups (57.0% and 42.9%, respectively); however, the differences were less for grade 3 or 4 CRS between the Asian subgroup (7.2%) and White or Other subgroups (3.9% and 0%, respectively). The incidences for serious TEAEs of CRS were lower in the Asian (26.1%) subgroup than in the White or Other subgroups (39.1% and 37.5%, respectively). One (0.3%) subject in the All B-NHL group with MCL had grade 4 CRS.

As shown in Table ***81***, the incidence of CRS (any grade) was higher in the Asian population across all safety pools presented, but it was the most pronounced in the LBCL cohort of Safety Pool 01+04 (Asian 76.1% vs White 51.6% and Other 32.3%). The latter was driven by the smaller GCT3013-04 trial which included only Asian patients, where an incidence of any grade CRS of >80% (88.9% in the Escalation part and 83.3% in the Expansion part) was observed in subjects receiving 48 mg epcoritamab. The race differences were less clear for grade 3 and higher CRS, although this must be interpreted with caution due to few observations (a total of 8 subjects in each of the White and Asian subgroups of the All B-NHL population).

Table 68: Overview of CRS by Race (48 mg Safety Analysis Set – Escalation + Expansion)

Number of Subjects, n (%)	Safety Pool 01+04								
	LBCL (N=208)			DLBCL (N=188)			All B-NHL (N=374)		
	White (N=106)	Asian (N=71)	Other (N=31)	White (N=93)	Asian (N=67)	Other (N=28)	White (N=207)	Asian (N=111)	Other (N=56)
Number of Subjects with ≥1:									
AESI									
CRS (All grade)	55 (51.9%)	54 (76.1%)	10 (32.3%)	47 (50.5%)	50 (74.6%)	10 (35.7%)	118 (57.0%)	88 (79.3%)	24 (42.9%)
Grade 3 and higher	3 (2.8%)	5 (7.0%)	0	3 (3.2%)	5 (7.5%)	0	8 (3.9%)	8 (7.2%)	0

Exposure-safety analyses suggest that there is no apparent relationship between PK and CRS. Therefore, the exposure-safety modelling data may indicate that the higher incidence of CRS in the Asian subgroup is not due to higher exposures to epcoritamab in Asian subjects, but rather due to other unidentified confounding factors. This is also supported by the subgroup analysis based on baseline body weight, indicating that body weight does not appear to affect the safety of epcoritamab treatment (see next section).

Baseline weight

There were no apparent weight-related trends in the frequency and severity of events across TEAE categories and the AESIs of CRS, CTLS, and ICANS in the Safety Pool 01+04 All B-NHL group (N=374). No weight-related trends were observed in the All B-NHL group for CRS, but a trend of lower incidences of CRS (all grades) was observed with increasing weight in LBCL subjects in Safety Pool 01+04 (N=208) (63.5% vs 57.7% vs 44.4%, respectively). The same trend was not observed for LBCL subjects in Safety Pool 01. According to the applicant, this is also confounded by the overall higher incidence of CRS in the GCT3013-04 and the trend towards lower subject weight. The median weight in the GCT3013-04 aNHL expansion cohort was 53.1 kg (range: 39.1, 87.2) compared to 70.2 kg (range: 39, 144) in Safety Pool 01. In addition, it is observed that the incidence of CRS in the <65 kg group in Safety Pool 01+04 LBCL (63.5%) was higher than that of the same weight group in Safety Pool 01 (50.0%). Hence, it is concluded that bodyweight does not appear to affect the safety of epcoritamab treatment based on the data currently available.

Baseline renal function

Renal function subgroups were based on creatinine clearance at baseline and included the following categories: normal (≥90 mL/min), mildly impaired (60 to <90 mL/min), moderately impaired (30 to < 60 mL/min), and severely impaired (15 to < 30 mL/min). In the Safety Pool 01+04 All B-NHL group (N=374), the frequency and severity of events were in general similar across TEAE and AESI categories, except for differences in incidence of ≥5% between the normal and mildly impaired renal function subgroups, respectively:

- Fatal TEAEs: 2.2% vs 8.1%
- CRS (all grades): 54.8% vs 65.2%

Similar trends were not observed for serious cases of CRS (34.1% vs 36.6% respectively) or grade 3 or 4 CRS (4.4% and 5.0%, respectively). Epcoritamab has not been studied in subjects with severe renal impairment. No treated subjects from GCT3013-01 and GCT3013-04 were classified with severe renal impairment at baseline.

Baseline hepatic function

Hepatic function subgroups were based on NCI criteria at baseline and included the following categories: normal, mild dysfunction, moderate dysfunction, severe dysfunction, and unknown. In the Safety Pool 01+04 All B-NHL group (N=374), at baseline, the majority of subjects (82.6%) had normal hepatic function and 15.5% of subjects had mild hepatic dysfunction. Some trends were observed of higher incidences across TEAE categories and the AESIs of CRS and ICANS in the mild dysfunction group compared to the normal group, respectively, with differences ≥5% between subgroups noted below:

- Serious TEAEs: 67.2% vs 57.3%
- TEAEs leading to dose delay: 46.6% vs 39.5%
- CRS (all grades): 70.7% vs 60.8%
- Grade 3 or 4 CRS: 8.6% vs 3.6%
- ICANS (all grades): 12.1% vs 5.2%

Results may be confounded by the potential for increased disease severity in subjects with impaired hepatic function according to the applicant. When comparing patients with mild baseline hepatic impairment at baseline and normal baseline hepatic function, patients with mild hepatic impairment more often had Stage IV disease and baseline liver involvement. Disease type at study entry, median years from initial diagnosis to first dose of epcoritamab, and incidence of subjects with ≥4 prior lines of anti-lymphoma therapy were similar between the subgroups of mild hepatic impairment and normal hepatic function at baseline. Epcoritamab has not been studied in subjects with severe hepatic impairment. No treated subjects from GCT3013-01 and GCT3013-04 were classified with severe hepatic dysfunction at baseline. Only 1 subject had moderately impaired hepatic function, and therefore, the impact of moderate hepatic impairment on safety is also unknown.

Ann Arbor staging

Subgroups were based on Ann Arbor staging at baseline and included the following categories: I/II and III/IV. In the Safety Pool 01+04 All B-NHL group (N=374), approximately 4 times the number of subjects were Ann Arbor stage III/IV at baseline (307 subjects; 82.1%) compared to stage I/II at baseline (67 subjects; 17.9%). Some trends were observed of higher incidences across TEAE categories and the AESIs of CRS and ICANS in the Ann Arbor stage III/IV group compared to the stage I/II group, respectively, with differences ≥5% between subgroups noted below:

- Grade 3 and higher TEAEs: 67.8% vs 59.7%
- Serious TEAEs: 61.6% vs 43.3%
- TEAEs leading to dose delay: 42.3% vs 31.3%
- CRS (all grades): 62.9% vs 55.2%
- Grade 3 or 4 CRS: 5.2% vs 0%
- ICANS (all grades): 7.5% vs 0%

Results are confounded by the potential for increased disease severity in subjects who were Ann Arbor stage III/IV at baseline according to the applicant.

CD20-negative disease

A total of 8 subjects in the GCT3013-01 Expansion Part aNHL cohort had tumour biopsies reported as CD20-negative based on local laboratory assessments. These patients were considered CD20-positive for study inclusion based on documented evidence of CD20-positivity based on representative pathology.

All 8 (100%) subjects experienced at least 1 TEAE, including 6 (75.0%) subjects who experienced TEAEs considered related to epcoritamab by the investigator. A total of 5 (62.5%) subjects experienced at least 1 Grade 3 or higher TEAE, and 3 (37.5%) subjects had Grade 3 or higher TEAEs considered related to epcoritamab by the investigator. Serious TEAEs were reported in 6 (75.0%) subjects and were considered related to epcoritamab in 5 (62.5%) subjects. Fatal TEAEs were reported in 1 (12.5%) subject, which was assessed as not related to epcoritamab by the investigator. TEAEs that led to treatment discontinuation and to dose delay were reported in 2 (25.0%) subjects each. AESIs of CRS were reported for 6 (75.0%) subjects; there were no events of ICANS or CTLS in these subjects. TEAEs reported in 2 or more of these 8 subjects included CRS in 6 subjects (75.0%), injection site reaction in 3 subjects (37.5%), and 2 subjects (25.0%) each for anemia, hypoalbuminemia, hyponatremia, pleural effusion, thrombocytopenia, thrombophlebitis, and vomiting.

Extrinsic factors

Geographic region

The largest proportion of subjects in Safety Pools 01 and 01+04 were from Europe. The GCT3013-04 trial enrolled only Asian subjects. In the Safety Pool 01+04 All B-NHL group (N=374), 14.2% of subjects were from North America, 48.1% from Europe, 28.3% from Asia, and 9.4% from other regions. The frequency and severity of events were generally similar between regions across all TEAE and AESI categories with the following exceptions:

- The use of dose delays for TEAE management was highest in Europe (50.0%) followed by other regions (37.1%), Asia (34.9%), and North America (20.8%).
- The incidence of serious TEAEs was >10% less in Asia (42.5%) than in Europe (67.2%), North America (56.6%), and other regions (62.9%).
- The incidence of CRS (all grades) was >10% higher in Asia (78.3%) than in Europe (56.7%), North America (47.2%), and other regions (57.1%).
- The incidence of grade 3 or higher TEAEs was >10% higher in Europe (66.1%), Asia (68.9%), and other (74.3%) than in North America (56.6%).

Prior lines of anti-lymphoma therapy

In the Safety Pool 01+04 All B-NHL group (N=374), 222 of 374 subjects (59.4%) received ≤ 3 lines of prior anti-lymphoma therapy and 152 (40.6%) subjects received >3 lines. In general, the frequency and severity of events were similar between subgroups across TEAE categories and the AESI of ICANS. CTLS was only observed in the ≤3 lines of prior anti-lymphoma therapy subgroup (2.3%; 5 subjects). Differences in incidence ≥5% between subjects who received ≤3 lines of prior anti-lymphoma therapy compared to subjects who received >3 lines of prior anti-lymphoma therapy, respectively, include:

- CRS (all grades): 68.0% vs 52.0%
- Serious TEAEs: 60.4% vs 55.3%

As shown in Table ***82***, the higher incidence of CRS in subjects with ≤3 prior lines of anti-lymphoma therapy compared to subjects with >3 lines of anti-lymphoma therapy in the Safety Pool 01+04 All B-NHL were not as apparent in any of the other safety pools.

Table 69: Overview of CRS by Prior Lines of Anti-lymphoma Therapies (48 mg Safety Analysis Set – Escalation + Expansion)

	Safety Pool 01				Safety Pool 01+04					
	LBCL (N=167)	DLBCL (N=148)			LBCL (N=208)	DLBCL (N=188)	All B-NHL (N=374)			
Number of Subjects, n (%)	≤3 (N=100)	>3 (N=67)	≤3 (N=92)	>3 (N=56)	≤3 (N=127)	>3 (N=81)	≤3 (N=118)	>3 (N=70)	≤3 (N=222)	>3 (N=152)
CRS (All grade)	52 (52.0%)	32 (47.8%)	46 (50.0%)	27 (48.2%)	75 (59.1%)	44 (54.3%)	68 (57.6%)	39 (55.7%)	151 (68.0%)	79 (52.0%)
Grade 3 and higher	2 (2.0%)	2 (3.0%)	2 (2.2%)	2 (3.6%)	3 (2.4%)	5 (6.2%)	3 (2.5%)	5 (7.1%)	10 (4.5%)	6 (3.9%)

Hence, the increased incidence of CRS in the ≤3 prior lines subgroup seems to be largely driven by an increased incidence in the non-LBCL (i.e., non-target) population of the All B-NHL pool. Overall, the safety profile does not seem to be worse in patients with more prior lines of therapy.

Prior treatment with CAR-T

In the Safety Pool 01+04 All B-NHL group (N=374), 83 (22.2%) subjects received prior CAR-T cell therapy. In general, the frequency and severity of events were similar between subgroups across TEAE categories and the AESIs with the exceptions of differences in CRS and TEAEs leading to dose delay. CTLS was only reported in subjects who did not have prior CAR-T cell therapy (1.7%; 5 subjects). Differences in incidence ≥5% between subjects who did not have prior CAR-T cell therapy compared to subjects who had prior CAR-T cell therapy, respectively, include:

- TEAEs leading to dose delay: 42.3% vs 33.7%
- CRS (all grades): 68.0% vs 38.6%

Smaller differences were observed for grade 3 or 4 CRS (4.5% vs 3.6%, respectively).

One trend occurred consistently across the different Safety Pools presented, namely that CRS (all grades) occurred with a higher incidence among those that had not received prior CAR-T cell therapy compared to subjects who had prior CAR-T cell therapy (58.8% vs 36.9% in the Safety Pool 01 (LBCL) population). It should be noted that few (n=2) subjects in the supportive GCT3013-04 trial were treated with CAR-T cell therapy prior to epcoritamab. Hence, the higher incidence of CRS in the cohort without prior CAR-T cell therapy may be confounded by the overall higher incidence of CRS in the GCT3013-04 trial.

2.6.8.7. Immunological events

Subjects included in the analysis were from the immunogenicity analysis set, which included all subjects exposed to epcoritamab who had an evaluable baseline ADA sample, and 1 or more evaluable on-treatment ADA samples. ADA was measured using different assays in the GCT3013-01 and GCT3013-04 trials; therefore, Safety Pool 01+04 data is not provided. In addition, an All B-NHL group from Safety Pool 01 was included in this analysis to provide a larger population for the GCT3013-01 trial.

ADA evaluable patient is defined as a patient from FAS with an evaluable baseline ADA sample and ≥1 evaluable on-treatment ADA sample.

The term indeterminate may refer to sample-level "indeterminate" value or patient-level "indeterminate" value. Sample-level indeterminate values refer to ADA-positive values with no confirmation (AVALCOMM = "Positive value with no confirmation yet"). Based on this definition, only 1 ADA sample was classified as indeterminate. For this sample, the screening ADA assay result was positive but confirmatory ADA assay could not be performed due to insufficient sample. A patient is classified as indeterminate for the following reason: A patient is classified as indeterminate if the patient is confirmed ADA positive at baseline but there is no confirmed positive on-treatment record or if confirmed ADA positive on treatment record titer are equal or lower than baseline.

Sampling for ADAs was performed in the escalation phase of study GCT3013-01 at screening, C1D15, C1D22, C2D1, C2D8, C2D15, C2D22, C3-6D1, C3-6D15, C7-PD D1, EOT. In the expansion phase ADA sampling took place at C1D1, C1D22, C2-3D1, C2-3D22, C4-9D1, C4-9D15, C10-PD D1, EOT.

Due to the low number of subjects with ADAs (
Table 83), a meaningful analysis of the impact of ADAs on safety is limited; therefore, brief summaries of safety information for each LBCL subject who was ADA on treatment positive are provided below.

Safety Pool 01: GCT3013-01 (ESC + EXP)

In the Safety Pool 01 LBCL group (N=158 [AIS]), 4 (2.5%) subjects were ADA positive at baseline. On treatment ADA status was positive for 4 (2.5%) subjects, of which only 1 subject (0.7%) had titer ≥1 (1:320 taking account of all dilutions). All had an onset of C1D22 or later. Due to the low risk for immunogenicity and the low incidence of samples positive for antibodies to epcoritamab, neutralizing antibodies were not evaluated at this time.

Of the 4 LBCL subjects who were ADA positive on treatment and not at baseline, 2 of the subjects discontinued treatment within the first 2 cycles due to progressive disease, and the other 2 subjects remained on treatment for an additional >10 cycles. Three of the four patients experienced TEAEs that were not related to epcoritamab according to the investigator, and the other patient experienced neutropenia considered to be related to epcoritamab which resolved with continuing epcoritamab treatment.

In the Safety Pool 01 All B-NHL group (N=258 [IAS]), 9 (3.5%) subjects were ADA positive at baseline. On treatment ADA status was positive for 8 (3.1%) subjects (
Table 83). Four subjects from the iNHL and MCL expansion cohorts were ADA positive on treatment in addition to the 4 LBCL subjects mentioned above.

Of the ADA evaluable subjects in the GCT3013-01 escalation and aNHL expansion cohorts, baseline positive ADA samples had titres of 0.5 (i.e., <1; 1:80 after accounting for dilutions). Similarly, the titres for all baseline positive ADA samples in the ADA evaluable subjects from GCT3013-01 iNHL and MCL expansion cohorts were 0.5 (i.e., <1), with the exception of two subjects from the GCT3013-01 MCL expansion cohort, one had a baseline titre value of 2 (actual titer ≤1:320 taking into account sample dilutions) and the other subject had a baseline titre value of 3 (actual titer ≤1:640 taking into account sample dilutions).

A considerable higher incidence of ADA positive patients are observed for the lower doses in the dose escalation part of study GCT3013-01 (32.4% [11/34] at the eight dose levels ≤6mg), with no definite pattern regarding at which doses ADAs were observed.

GCT3013-04

Of the 2 subjects who were ADA positive on treatment and not at baseline in the GCT3013-04 trial, both subjects remained on treatment.

In GCT3013-04 DLBCL subjects (N=39 [IAS]), 1 (2.6%) subject was ADA positive at baseline. On treatment ADA status was positive for 1 (2.6%) subject with titer <1 at the C6D15 visit (Table 83). The subject had a concurrent TEAE of grade 1 injection site reaction that was considered related to study treatment by the investigator, and which resolved following topical treatment. The subject continued treatment and was ongoing in C13 of treatment at the time of the data cutoff.

In GCT3013-04 All B-NHL subjects (N=60 [IAS]), 1 (1.7%) subject was ADA positive at baseline. On treatment status was positive for 2 (3.3%) subjects (Table 83). One subject was from the DLBCL expansion cohort (described above) and the other subject was from the FL expansion cohort with titer <1 at the C1D22 visit that resolved and the subject continued epcoritamab treatment.

In the dose escalation part of GCT3013-04 (all dose levels), all subjects were ADA negative at baseline. In expansion Part of GCT3013-04, at the proposed dose regimen, from the DLBCL subjects (N=39) that received ≥1 dose of epcoritamab and had ≥1 analyzed immunogenicity sample after receiving epcoritamab, only 1 subject was ADA-positive at baseline (titre value <1). Similarly, from the FL subjects (N=20) that received ≥1 dose of epcoritamab and had ≥1 analyzed immunogenicity sample after receiving epcoritamab in the expansion part of GCT3013-04 at the proposed dose regimen, no subject was ADA-positive at baseline.

Table 70: Summary of Antidrug Antibody Assessment (48 mg Immunogenicity Analysis Set)

	GCT3013-01			GCT3013-04	
	LBCL (N=158) n (%)	DLBCL (N=140) n (%)	All B-NHL (N=258) n (%)	DLBCL N=39 n (%)	All B-NHL N=60 n (%)
Baseline ADA positive [a]	**4 (2.5%)**	**4 (2.9%)**	**9 (3.5%)**	**1 (2.6%)**	**1 (1.7%)**
On-treatment ADA status [a]					
Positive	4 (2.5%)	4 (2.9%)	8 (3.1%)	1 (2.6%)	2 (3.3%)
Negative	150 (94.9%)	132 (94.3%)	241 (93.4%)	37 (94.9%)	57 (95.0%)
Indeterminate	4 (2.5%)	4 (2.9%)	9 (3.5%)	1 (2.6%)	1 (1.7%)
Titer out of on-treatment ADA positive sample [a, b]					
<1	3 (1.9%)	3 (2.1%)	7 (2.7%)	1 (2.6%)	1 (1.7%)
≥1	1 (0.6%)	1 (0.7%)	1 (0.4%)	0	1 (1.7%)

Abbreviations: ADA = anti-drug antibody; B-NHL = B-cell non-Hodgkin lymphoma; DLBCL = diffuse large B-cell lymphoma; iNHL = indolent B-cell non-Hodgkin lymphoma; LBCL = large B-cell lymphoma; MCL = mantle cell lymphoma.

Note: All B-NHL is composed of the LBCL population plus subjects with iNHL and MCL from the escalation and expansion parts of the trials. Percentages calculated based on N.

Note: For on-treatment results, a subject is considered ADA positive if either 1) ADA is negative at baseline and at least one on-treatment result is positive 2) positive at baseline and at least one positive on-treatment result with a titer higher than baseline.

Note: Only subjects who have been assigned and received at least one dose of epcoritamab at the 48 mg are included.

[a] CD3 or CD20 positive for GCT3013-04 subjects.

[b] The highest titer value will be summarized for subjects with on-treatment positive ADA sample(s).

Data cutoff date:31 Jan 2022

2.6.8.8. Safety related to drug-drug interactions and other interactions

Exploratory safety analysis was performed by evaluating grade 3 or 4 TEAEs in subjects who received the 48 mg full dose in Studies GCT3013-01 and GCT3013-04 and received a concomitant medication with a narrow therapeutic index (NTI) within 2 weeks of at least one episode of CRS event. The NTI drugs included: carbamazepine, cyclosporine, digoxin, divalproex sodium, everolimus, levothyroxine, liothyronine, phenytoin, sirolimus, theophylline, warfarin, valproate sodium, tacrolimus, valproic acid, rapamycin.

The limited data indicated that there was no evidence that subjects receiving concomitant medications with a narrow therapeutic index within a 2 - week period of a CRS episode had different rates of grade 3 and 4 TEAEs compared to the overall epcoritamab population (Table 84).

Table 71: Grade 3 or 4 Treatment-Emergent Adverse Events in Subjects who Received a Concomitant Medication With a Narrow Therapeutic Index Within 2 Weeks of at Least 1 Episode of CRS Event (48 mg Dose - GCT3013-01 and GCT3013-04 - Safety Analysis Set)

Number of Subjects, n (%)	GCT3013-01 ESC+EXP		GCT3013-01+GCT3013-04 ESC+EXP		
System Organ Class Preferred Term	LBCL (N=2)	DLBCL (N=2)	LBCL (N=2)	DLBCL (N=2)	All B-NHL (N=4)
Blood and lymphatic system disorders	**1 (50.0%)**	**1 (50.0%)**	**1 (50.0%)**	**1 (50.0%)**	**2 (50.0%)**
Lymphopenia	1 (50.0%)	1 (50.0%)	1 (50.0%)	1 (50.0%)	1 (25.0%)
Thrombocytopenia	1 (50.0%)	1 (50.0%)	1 (50.0%)	1 (50.0%)	1 (25.0%)
Anaemia	0	0	0	0	1 (25.0%)
Neutropenia	0	0	0	0	1 (25.0%)
Immune system disorders	**1 (50.0%)**	**1 (50.0%)**	**1 (50.0%)**	**1 (50.0%)**	**2 (50.0%)**
Cytokine release syndrome	1 (50.0%)	1 (50.0%)	1 (50.0%)	1 (50.0%)	2 (50.0%)
Vascular disorders	**1 (50.0%)**	**1 (50.0%)**	**1 (50.0%)**	**1 (50.0%)**	**2 (50.0%)**
Hypotension	1 (50.0%)	1 (50.0%)	1 (50.0%)	1 (50.0%)	1 (25.0%)
Hypovolaemic shock	0	0	0	0	1 (25.0%)
Cardiac disorders	**0**	**0**	**0**	**0**	**1 (25.0%)**
Atrial fibrillation	0	0	0	0	1 (25.0%)
Gastrointestinal disorders	**0**	**0**	**0**	**0**	**1 (25.0%)**
Upper gastrointestinal haemorrhage	0	0	0	0	1 (25.0%)
General disorders and administration site conditions	**0**	**0**	**0**	**0**	**1 (25.0%)**
Multiple organ dysfunction syndrome	0	0	0	0	1 (25.0%)
Infections and infestations	**0**	**0**	**0**	**0**	**1 (25.0%)**
Infectious pleural effusion	0	0	0	0	1 (25.0%)

Abbreviations: ADA = anti-drug antibody; B-NHL = B-cell non-Hodgkin lymphoma; CRS = cytokine release syndrome; DLBCL = diffuse large B-cell lymphoma; ESC = escalation; EXP = expansion; iNHL = indolent B-cell non-Hodgkin lymphoma; LBCL = large B-cell lymphoma; MCL = mantle cell lymphoma; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SOC = system organ class.

Note: Percentages calculated based on N.

Note: Adverse events are classified using MedDRA v24.1 and are counted only once per system organ class and only once per preferred term.

Source: Table 3.19 (Data Cutoff: 31 Jan 2022; Date Generated: 09JUN2022 07:34)

Epcoritamab causes transient and modest release of cytokines that may potentially suppress CYP450 enzymes. The peak median IL-6 concentration was 21.5 pg/mL on C1D16 (following administration of the first full dose of 48 mg on C1D15) in subjects with LBCL in the aNHL expansion cohort of the GCT3013-01 trial. In addition, exploratory assessment in 4 subjects who received sensitive CYP450 substrates with a narrow therapeutic index within 2 weeks of a CRS episode showed no apparent difference in rates of grade 3 and 4 TEAEs compared to the overall population. Therefore, the risk of drug interaction is considered low.

Given the technical challenges of conducting a dedicated drug-drug interaction trial to coincide with the peak of cytokine release and expected variance in degree of cytokine increase for individual subjects, no formal drug-drug interaction trial is considered feasible to assess the drug interaction potential due to cytokine release after epcoritamab treatment.

2.6.8.9. Discontinuation due to adverse events

Adverse events leading to treatment discontinuation

All TEAEs leading to permanent treatment discontinuation are summarized for all groups in Table 85. Most of these TEAEs were not considered treatment related by the investigator.

Safety Pool 01: GCT3013-01 (ESC + EXP)

In the Safety Pool 01 LBCL group (N=167), 13 (7.8%) subjects discontinued treatment due to at least 1 TEAE, and 3 (1.8%) discontinued treatment due to at least 1 TEAE considered related to epcoritamab by the investigator (Table 85). The only TEAEs leading to treatment discontinuation reported for more than 1 subject were COVID-19, COVID-19 pneumonia, and MDS in 2 (1.2%) subjects each. Treatment-related TEAEs leading to treatment discontinuation included CRS, ICANS, and CLIPPERS in 1 (0.6%) subject each. The ICANS was fatal and is discussed in the section on fatal events.

Safety Pool 01+04: GCT3013-01 (ESC + EXP) + GCT3013-04 (ESC + EXP)

In the Safety Pool 01+04 All B-NHL group (N=374), 24 (6.4%) subjects discontinued treatment due to at least 1 TEAE, and 6 (1.6%) discontinued treatment due to at least 1 TEAE considered related to epcoritamab by the investigator (Table 85). TEAEs leading to treatment discontinuation reported in more than 1 subject were COVID-19 pneumonia in 3 (0.8%) subjects and CRS, COVID-19, and MDS in 2 (0.5%) subjects each. Treatment-related TEAEs leading to treatment discontinuation included CRS in 2 (0.5%) subjects; and ICANS, CLIPPERS, sepsis, enteritis, and multiple organ dysfunction syndrome in 1 (0.3%) subject each.

Table 72: All Treatment-Emergent Adverse Events Leading to Treatment Discontinuation by SOC and PT (48 mg Safety Analysis Set – Escalation + Expansion)

System Organ Class Preferred Term, n (%)	Safety Pool 01				Safety Pool 01+04					
	LBCL (N=167)		DLBCL (N=148)		LBCL (N=208)		DLBCL (N=188)		All B-NHL (N=374)	
	All	Related	All	Related	All	Related	All	Related	All	Related
Subjects with ≥1 TEAE leading to treatment discontinuation	**13 (7.8%)**	**3 (1.8%)**	**12 (8.1%)**	**3 (2.0%)**	**15 (7.2%)**	**3 (1.4%)**	**14 (7.4%)**	**3 (1.6%)**	**24 (6.4%)**	**6 (1.6%)**
Infections and infestations	**5 (3.0%)**	**0**	**5 (3.4%)**	**0**	**5 (2.4%)**	**0**	**5 (2.7%)**	**0**	**9 (2.4%)**	**1 (0.3%)**
COVID-19	2 (1.2%)	0	2 (1.4%)	0	2 (1.0%)	0	2 (1.1%)	0	2 (0.5%)	0
COVID-19 pneumonia	2 (1.2%)	0	2 (1.4%)	0	2 (1.0%)	0	2 (1.1%)	0	3 (0.8%)	0
Progressive multifocal leukoencephalopathy	1 (0.6%)	0	1 (0.7%)	0	1 (0.5%)	0	1 (0.5%)	0	1 (0.3%)	0
Pneumonia	0	0	0	0	0	0	0	0	1 (0.3%)	0
Sepsis	0	0	0	0	0	0	0	0	1 (0.3%)	1 (0.3%)
Septic shock	0	0	0	0	0	0	0	0	1 (0.3%)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**3 (1.8%)**	**0**	**3 (2.0%)**	**0**	**5 (2.4%)**	**0**	**5 (2.7%)**	**0**	**6 (1.6%)**	**0**
Myelodysplastic syndrome	2 (1.2%)	0	2 (1.4%)	0	2 (1.0%)	0	2 (1.1%)	0	2 (0.5%)	0

System Organ Class Preferred Term, n (%)	Safety Pool 01				Safety Pool 01+04					
	LBCL (N=167)		DLBCL (N=148)		LBCL (N=208)		DLBCL (N=188)		All B-NHL (N=374)	
	All	Related	All	Related	All	Related	All	Related	All	Related
Chronic myelomonocytic leukaemia	0	0	0	0	1 (0.5%)	0	1 (0.5%)	0	1 (0.3%)	0
Lung neoplasm	1 (0.6%)	0	1 (0.7%)	0	1 (0.5%)	0	1 (0.5%)	0	1 (0.3%)	0
Pancreatic carcinoma	0	0	0	0	1 (0.5%)	0	1 (0.5%)	0	1 (0.3%)	0
Angioimmunoblastic T-cell lymphoma	0	0	0	0	0	0	0	0	1 (0.3%)	0
General disorders and administration site conditions	**2 (1.2%)**	**0**	**2 (1.4%)**	**0**	**2 (1.0%)**	**0**	**2 (1.1%)**	**0**	**3 (0.8%)**	**1 (0.3%)**
Fatigue	1 (0.6%)	0	1 (0.7%)	0	1 (0.5%)	0	1 (0.5%)	0	1 (0.3%)	0
General physical health deterioration	1 (0.6%)	0	1 (0.7%)	0	1 (0.5%)	0	1 (0.5%)	0	1 (0.3%)	0
Multiple organ dysfunction syndrome	0	0	0	0	0	0	0	0	1 (0.3%)	1 (0.3%)
Nervous system disorders	**2 (1.2%)**	**2 (1.2%)**	**2 (1.4%)**	**2 (1.4%)**	**2 (1.0%)**	**2 (1.0%)**	**2 (1.1%)**	**2 (1.1%)**	**2 (0.5%)**	**2 (0.5%)**
Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids	1 (0.6%)	1 (0.6%)	1 (0.7%)	1 (0.7%)	1 (0.5%)	1 (0.5%)	1 (0.5%)	1 (0.5%)	1 (0.3%)	1 (0.3%)
Immune effector cell-associated neurotoxicity syndrome	1 (0.6%)	1 (0.6%)	1 (0.7%)	1 (0.7%)	1 (0.5%)	1 (0.5%)	1 (0.5%)	1 (0.5%)	1 (0.3%)	1 (0.3%)
Immune system disorders	**1 (0.6%)**	**1 (0.6%)**	**1 (0.7%)**	**1 (0.7%)**	**1 (0.5%)**	**1 (0.5%)**	**1 (0.5%)**	**1 (0.5%)**	**2 (0.5%)**	**2 (0.5%)**
Cytokine release syndrome	1 (0.6%)	1 (0.6%)	1 (0.7%)	1 (0.7%)	1 (0.5%)	1 (0.5%)	1 (0.5%)	1 (0.5%)	2 (0.5%)	2 (0.5%)
Respiratory, thoracic and mediastinal disorders	**1 (0.6%)**	**0**	**0**	**0**	**1 (0.5%)**	**0**	**0**	**0**	**2 (0.5%)**	**0**
Pleural effusion	1 (0.6%)	0	0	0	1 (0.5%)	0	0	0	1 (0.3%)	0
Dyspnoea	0	0	0	0	0	0	0	0	1 (0.3%)	0
Ear and labyrinth disorders	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**1 (0.3%)**	**0**
Deafness	0	0	0	0	0	0	0	0	1 (0.3%)	0
Gastrointestinal disorders	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**2 (0.5%)**	**1 (0.3%)**
Diarrhoea	0	0	0	0	0	0	0	0	1 (0.3%)	0
Enteritis	0	0	0	0	0	0	0	0	1 (0.3%)	1 (0.3%)

Abbreviations: B-NHL = B-cell non-Hodgkin lymphoma; COVID-19 = coronavirus disease 2019; DLBCL = diffuse large B-cell lymphoma; iNHL = indolent B-cell non-Hodgkin lymphoma; LBCL = large B-cell lymphoma; MCL = mantle cell lymphoma; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SOC = system organ class; TEAE = treatment-emergent adverse event.
Note: Safety Pool 01 includes GCT3013-01. Safety Pool 01+04 includes GCT3013-01 and GCT3013-04. All B-NHL is composed of the LBCL population plus subjects with iNHL (n=128) and MCL (n=38) from the escalation and expansion parts of the trials. Percentages calculated based on N. Sorted by descending frequency in the Safety Pool 01+04 LBCL All column.
Note: Adverse events are classified using MedDRA v24.1 and are counted only once per system organ class and only once per preferred term.
Data cutoff date:31 Jan 2022
Source: Table 3.10

Adverse events leading to dose delay

Safety Pool 01: GCT3013-01 (ESC + EXP)

In the Safety Pool 01 LBCL group (N=167), 60 (35.9%) subjects experienced at least 1 TEAE leading to dose delay, and 29 (17.4%) subjects had events that were considered treatment-related by the investigator (Table 86). The most frequently reported (≥2%) TEAEs that led to dose delay were CRS (7.2%); neutropenia (4.2%); pyrexia (3.0%); and acute kidney injury, pleural effusion, and thrombocytopenia (2.4% each).

Safety Pool 01+04: GCT3013-01 (ESC + EXP) + GCT3013-04 (ESC + EXP)

Adverse events leading to dose delay were similar to those reported above for Safety Pool 01.

Table 73: Treatment-Emergent Adverse Events Leading to Dose Delay Reported for ≥2% of Subjects in Any Group by SOC and PT (48 mg Safety Analysis Set – Escalation + Expansion)

System Organ Class Preferred Term, n (%)	Safety Pool 01				Safety Pool 01+04					
	LBCL (N=167)		DLBCL (N=148)		LBCL (N=208)		DLBCL (N=188)		All B-NHL (N=374)	
	All	Related	All	Related	All	Related	All	Related	All	Related
Subjects with ≥1 TEAE leading to dose delay	60 (35.9%)	29 (17.4%)	51 (34.5%)	23 (15.5%)	76 (36.5%)	44 (21.2%)	67 (35.6%)	38 (20.2%)	151 (40.4%)	82 (21.9%)
Infections and infestations	22 (13.2%)	1 (0.6%)	20 (13.5%)	1 (0.7%)	28 (13.5%)	6 (2.9%)	26 (13.8%)	6 (3.2%)	63 (16.8%)	13 (3.5%)
Urinary tract infection	2 (1.2%)	0	2 (1.4%)	0	4 (1.9%)	1 (0.5%)	4 (2.1%)	1 (0.5%)	7 (1.9%)	1 (0.3%)
COVID-19	3 (1.8%)	0	3 (2.0%)	0	3 (1.4%)	0	3 (1.6%)	0	10 (2.7%)	1 (0.3%)
Immune system disorders	12 (7.2%)	12 (7.2%)	8 (5.4%)	8 (5.4%)	15 (7.2%)	15 (7.2%)	11 (5.9%)	11 (5.9%)	29 (7.8%)	29 (7.8%)
Cytokine release syndrome	12 (7.2%)	12 (7.2%)	8 (5.4%)	8 (5.4%)	15 (7.2%)	15 (7.2%)	11 (5.9%)	11 (5.9%)	29 (7.8%)	29 (7.8%)
Blood and lymphatic system disorders	**12 (7.2%)**	**8 (4.8%)**	**12 (8.1%)**	**8 (5.4%)**	**13 (6.3%)**	**9 (4.3%)**	**13 (6.9%)**	**9 (4.8%)**	**29 (7.8%)**	**18 (4.8%)**
Neutropenia	7 (4.2%)	6 (3.6%)	7 (4.7%)	6 (4.1%)	8 (3.8%)	7 (3.4%)	8 (4.3%)	7 (3.7%)	16 (4.3%)	12 (3.2%)
Thrombocytopenia	4 (2.4%)	1 (0.6%)	4 (2.7%)	1 (0.7%)	4 (1.9%)	1 (0.5%)	4 (2.1%)	1 (0.5%)	10 (2.7%)	5 (1.3%)
Investigations	5 (3.0%)	2 (1.2%)	4 (2.7%)	1 (0.7%)	12 (5.8%)	9 (4.3%)	11 (5.9%)	8 (4.3%)	22 (5.9%)	14 (3.7%)
Neutrophil count	0	0	0	0	4	4	4	4	5	4

System Organ Class Preferred Term, n (%)	Safety Pool 01				Safety Pool 01+04					
	LBCL (N=167)		DLBCL (N=148)		LBCL (N=208)		DLBCL (N=188)		All B-NHL (N=374)	
	All	Related	All	Related	All	Related	All	Related	All	Related
decreased					(1.9%)	(1.9%)	(2.1%)	(2.1%)	(1.3%)	(1.1%)
General disorders and administration site conditions	6 (3.6%)	1 (0.6%)	6 (4.1%)	1 (0.7%)	6 (2.9%)	1 (0.5%)	6 (3.2%)	1 (0.5%)	20 (5.3%)	10 (2.7%)
Pyrexia	5 (3.0%)	0	5 (3.4%)	0	5 (2.4%)	0	5 (2.7%)	0	10 (2.7%)	2 (0.5%)
Nervous system disorders	6 (3.6%)	3 (1.8%)	6 (4.1%)	3 (2.0%)	6 (2.9%)	3 (1.4%)	6 (3.2%)	3 (1.6%)	13 (3.5%)	6 (1.6%)
Immune effector cell-associated neurotoxicity syndrome	3 (1.8%)	3 (1.8%)	3 (2.0%)	3 (2.0%)	3 (1.4%)	3 (1.4%)	3 (1.6%)	3 (1.6%)	5 (1.3%)	5 (1.3%)
Respiratory, thoracic and mediastinal disorders	6 (3.6%)	0	5 (3.4%)	0	6 (2.9%)	0	5 (2.7%)	0	11 (2.9%)	1 (0.3%)
Pleural effusion	4 (2.4%)	0	3 (2.0%)	0	4 (1.9%)	0	3 (1.6%)	0	4 (1.1%)	0
Renal and urinary disorders	4 (2.4%)	0	1 (0.7%)	0	5 (2.4%)	1 (0.5%)	2 (1.1%)	1 (0.5%)	6 (1.6%)	1 (0.3%)
Acute kidney injury	4 (2.4%)	0	1 (0.7%)	0	4 (1.9%)	0	1 (0.5%)	0	5 (1.3%)	0

Abbreviations: B-NHL = B-cell non-Hodgkin lymphoma; COVID-19 = coronavirus disease 2019; DLBCL = diffuse large B-cell lymphoma; iNHL = indolent B-cell non-Hodgkin lymphoma; LBCL = large B-cell lymphoma; MCL = mantle cell lymphoma; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SOC = system organ class; TEAE = treatment-emergent adverse event.

Note: Safety Pool 01 includes GCT3013-01. Safety Pool 01+04 includes GCT3013-01 and GCT3013-04. All B-NHL is composed of the LBCL population plus subjects with iNHL (n=128) and MCL (n=38) from the escalation and expansion parts of the trials. Percentages calculated based on N. Sorted by descending frequency in the Safety Pool 01+04 LBCL All column.

Note: Adverse events are classified using MedDRA v24.1 and are counted only once per system organ class and only once per preferred term.

Data cutoff date:31 Jan 2022

Source: Table 3.9

Medication errors

A summary of medication errors in the program were evaluated. A total of 4 medication errors were summarized in the SCS.

Table 74. Summary of Medication Errors in the Epcoritamab DLBCL Program

Study [Phase or Study Arm]	Subject Age Range/ Gender]	PT(s) [Serious/ Grade]	SD Onset/End	Intended Dose / Actual Dose Administered [Overdose >10%]	AEs or SAEs	Dilution Method (vial or syringe)	Stage of Medication Use Process	Contributing Factors
Medication errors in Study GCT3013-01								
GCT3013-01 [ESC]	[70-80/F]	Incorrect dose administered [No/1]	1/1	0.08 mg / 0.96 mg [Yes]	None reported	Vial	Preparation – pharmacy used 60 mg/mL vial instead of 5 mg/mL	Human behavior
GCT3013-01 [ESC]	[70-80/M]	Incorrect dose administered [No/1]	540/540	60 mg / 57 mg [No]	None reported	N/A (no dilution required)	Dispensing – IVRS programming issue that dispensed 0.8 mL instead of 1.0 mL vial	System related

AE = adverse event; Arm 1 = epcoritamab + R-CHOP; ESC = escalation; F = female; IVRS = Interactive Voice Response System; M = male; N/A = not applicable; PT = preferred terms; SAE = serious adverse event; SCS = summary of clinical safety; SD = Study Day; SAE = serious adverse event;

2.6.8.10. Post marketing experience

N/A

2.6.9. Discussion on clinical safety

More than 700 patients with haematological malignancies have been exposed to epcoritamab in clinical studies as of the data cutoff date of 31 Jan 2022. The clinical development consists of 5 clinical studies. Study GCT3013-02 investigates combination therapies and study GCT3013-03 included only a small number of chronic lymphocytic leukemia (CLL) and Richter's syndrome (RS) patients so far. Study GCT3013-05 is proposed as confirmatory trial in the context of a CMA and the data is currently blinded. Studies GCT3013-01 and GCT3013-04 in patients with B-cell lymphoma are the basis for the safety analysis and this is agreed. Five additional months of safety data (data cutoff date of 30 June 2022) from the GCT3013-01 and GCT3013-04 studies were provided upon request. Very few patients with ECOG of 2 or higher were included, which results in a study population which has a relatively good performance status.

Safety pools- In studies GCT3013-01 and GCT3013-04, 374 patients with B-cell lymphomas were treated with the proposed posology of 48 mg full dose after a priming and intermediate dose. The **primary safety analysis pool** (study 01 LBCL) includes the patients in study GCT3013-01 with large B-cell lymphoma (LBCL) (n=167, 148 with diffuse LBCL (DLBCL)). The **supportive safety analysis pool** (studies 01+04 All B-NHL) consists of all B-cell non-Hodgkin lymphoma (B-NHL) patients treated with 48 mg epcoritamab in studies GCT3013-01 and GCT3013-04: 374 patients with 208 LBCL (of which 188 DLBCL), 128 indolent NHL (iNHL), and 38 mantle cell lymphoma (MCL). Other pools provided are the DLBCL group of study GCT3013-01; and the LBCL and DLBCL groups of studies GCT3013-01 and GCT3013-04 combined. The proposed pooling strategy is endorsed. It should be noted that the supportive safety analysis pool also includes the full primary safety pool (167/374

patients, 44.6%). Hence, the safety results for the "All B-NHL" population are largely influenced by the results of the primary safety population.

The updated safety analysis (DCO 30 June 2022) included no new subjects in the primary safety pool, but 57 additional subjects in the supportive safety pool. With the exception of COVID-19-related events, the overall safety profile of epcoritamab reported in the safety update was generally consistent with the reporting in the original submission. The results presented in this overview are derived from the initial analysis (DCO 31 Jan 2022) unless otherwise stated. The frequencies of adverse reactions provided in the SmPC section 4.8 reflect the most recent safety analyses (DCO 30 June 2022).

In the **primary safety analysis pool** median treatment duration was 3.7 months with 41.3% being treated for 6 months and 18.0% for 12 months. At the original data cutoff, 31.7% were still on study treatment. In 37.1% of patients a dose delay was required. The most common reason for discontinuation was disease progression and in 7.2% discontinuation was due to an TEAE. In the **supportive safety analysis pool** the numbers were overall similar, except that the proportion of patients still receiving epcoritamab was higher (46.8%) and discontinuations due to disease progression lower, which can be explained by the inclusion of patients with less aggressive disease. The median safety follow-up time was 5.6 months (range: <1 to 20 months) in the primary GCT3013-01 ESC+EXP R/R LBCL analysis set and 4.7 months (range: <1 to 20 months) in the supportive GCT3013-01+GCT3013-04 ESC+EXP All B-NHL analysis set. Given the short treatment exposure compared to the DoR of ~12 months and that epcoritamab should be administered until disease progression or unacceptable toxicity, it is agreed that long-term safety is included as missing information in the safety concerns and final CSRs will be provided post-marketing (see Annex II of the PI).

Regarding the presentation of epcoritamab, it is noted that a presentation of 4 mg epcoritamab per vial for administration is needed for preparation of 0.16 mg priming dose or 0.8 mg intermediate dose, but only a fraction of 4 mg is needed for preparation of the intended doses. This may lead to medication errors or multiple used of the content of the vial. Based on the information provided, two cases were identified in whom an overdose of >10% occurred with the priming/intermediate dose. In one case the wrong vial was used and in the other case there was a dilution error. The last case is of special interest, as the dilution error occurred with the 0.16 mg dosing and the overdose led to headache and chills. This case was identified in a different study than the 01 and 04 studies which are the basis of the MAA. However, this case is still of relevance as it supports the concern that the 4 mg /0.8ml presentation is less suitable for preparation of the 0.16 mg priming dose and 0.8 mg intermediate dose, even in the controlled setting of a clinical trial. With the 4 mg /0.8ml presentation only a fraction of it is needed for preparation of the injection for the priming and intermediate dose and a two-step dilution is needed for preparation of the 0.16 mg dose. This may lead to medication errors, which is thus already observed in the well-controlled clinical trial setting, with the post-marketing use by default being less controlled. The wording in SmPC section 6.6 instructions aims to mitigate the risk of "risk of overdose due to medication errors" has been included as important potential risk in the RMP. The SmPC also includes recommendations in section 4.2 about re-priming in case of delayed doses, which are in line with the approach used in the GCT3013-01 study and are based on popPK modeling. Lower exposures tend to be underestimated by the popPK model, however the model estimated "safe re-priming windows" are not fully reflected in the SmPC recommendations, which represent a much more conservative and simplified approach. The SmPC recommendations are supported by further popPK simulations and a repeated time-to-event (rTTE) modeling approach. The potential impact of the current re-priming recommendations on efficacy is however difficult to evaluate based on available data. The priming doses are used, to mitigate the risk of CSR. Considering that the currently proposed re-priming recommendations are in line with those used in the pivotal clinical study, this issue is not

further pursued. However, the applicant is encouraged to reassess the re-priming recommendations as more clinical data becomes available.

Adverse events- Almost all patients in the **primary safety analysis pool** experienced at least 1 TEAE (99%; related 83.8%). Grade ≥3 TEAEs occurred in 62.9% (related 28.1%). Serious TEAEs were observed in 58.1% (related 36.5%). In 7.2% a fatal TEAE was reported, one case of grade 5 ICANS was considered to be related to epcoritamab. TEAEs leading to treatment discontinuations occurred in 7.8% and to dose delay in 35.9%. AEs of special interest (AESI) will be discussed in further detail below, but were overall reported in 50.3% (Grade ≥3 in 2.4%), 6.0% (Grade ≥3 in 0.6%), and 1.2% (Grade ≥3 in 1.2%), respectively. In the **supportive safety analysis pool**, the overall safety profile was similar, except for a higher incidence of Grade ≥3 related TEAEs and (Grade ≥3) CRS in study GCT3013-04. The majority of all TEAEs, Grade ≥3 TEAEs, and serious AEs were reported as recovered/resolved.

The **most common TEAEs** occurring in ≥10% of patients in the **primary safety analysis pool** were CRS (50.3%); fatigue (24.6%); pyrexia (22.8%); injection site reaction (IRR) and neutropaenia (22.2% each); nausea (20.4%), diarrhoea (19.8%); anaemia (18.0%); abdominal pain (13.8%); thrombocytopaenia (13.2%); headache (12.6%); constipation and vomiting (12.0% each); decreased appetite and oedema peripheral (11.4% each); and back pain and insomnia (10.8% each). For the **supportive safety analysis pool** the most common TEAEs were similar, but CRS and IRR occurred more often in the supportive safety analysis pool mainly driven by the high rates reported in the DLBCL patients in study GCT3013-04. Most TEAEs occurred in the first 8 week period of study treatment, except for the SOC Infections and infestations with similar incidence in the overall treatment period and updated data on infections are requested (see later for the discussion on serious infections).

In the **primary safety analysis pool** of patients with at least 1 TEAE, 36.6 experienced an TEAE with worst Grade 1 or 2, 55.7% worst Grade 3 or 4, and 7.2% worst Grade 5. Cytopaenias were the only **Grade ≥3 TEAEs** reported in ≥5% of patients: Grade 3/4 neutropaenia in 15.6%, anaemia in 10.2%, and neutrophil count deceased and thrombocytopaenia in 6.0%. In the **supportive safety analysis pool**, cytopaenias were also the only Grade ≥3 TEAEs reported in ≥5% of patients.

In the **primary safety analysis pool** 83.8% reported ≥1 TEAE which was considered to be **related to the treatment** by the investigator (28.1% related Grade ≥3 TEAE). Most common treatment related TEAEs were CRS (50.3%), injection site reaction (22.2%), neutropaenia (18.0%), fatigue (15.0%), and pyrexia (11.4%). Most common Grade ≥3 treatment-related TEAEs were cytopaenias and CRS: neutropaenia (11.4%), neutrophil count deceased (3.6%), anaemia (2.4%), and CRS (2.4%). In the **supportive safety analysis pool**, the proportion of patients with related TEAEs was similar, but the proportion of patients Grade ≥3 related TEAE was higher with 38.8% mainly driven by the high rates reported in the DLBCL patients in study GCT3013-04. The type of reported treatment-related TEAEs was similar, but again CRS and IRS occurred more often. Regarding the differences observed, it is acknowledged that the number of patients from the GCT3013-04 study are limited. It is noted that the patients included in the GCT3013-04 study differ from the patients in the GCT3013-01 study, for example regarding gender, geographic region, and prior CAR-T cell use. In addition, the guidelines regarding hospitalization within the study were different. Hospitalization from C1D1 to C1D28 was specified in the protocol for the Dose Escalation Part, and for at least 24 hours following the first full dose (C1D15) in the Expansion Part of study GCT3013-04, which could be extended at the discretion of the investigator. Investigators tended to prolong subject hospitalization during C1 in the Expansion Part. As mentioned below, the incidence of CRS was approximately 10-20% higher between subgroups in each category for female patients, Asian patients, patients treated in Asia, and in patients without prior CAR-T cell therapy. The differences in study population in combination with the limited number of patients might (partly) explain the higher incidence of CRS in the GCT3013-04 study. The higher incidence of Grade 3 or 4 related AEs in the GCT3013-04 study were mainly driven by cytopaenias. The

reason for this and the higher incidence of injections site reactions is not fully understood, but might be influenced by differences in the study population, hospitalization around epcoritamab administration with possibly more close monitoring, and/or management of AEs.

AESI- Based on the mechanism of action (MoA), cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), and clinical tumor lysis syndrome (CTLS) were defined as AESI. CRS and ICANS are proposed by the applicant as important identified risks. The applicant proposes to manage and minimize these risks in the SmPC and additional educational materials. The SmPC includes information on premedication (section 4.2), dose modification and management guidance (section 4.2), warnings (section 4.4), and description of selected adverse events (section 4.8) for both CRS and ICANS, which are overall acceptable but amendments are requested (see SmPC assessment and LoQ). Tumour lysis syndrome is also included as a warning in section 4.4 of the SmPC.

CRS- For the **subject level analysis** (patients with multiple CRS event were counted only once), the incidence of CRS was numerically lower in the primary safety analysis pool (50.3%) than in the safety analysis pool with all LBCL and All B-NHL patients (57.2% and 61.5%, respectively). In the primary safety analysis pool, 2.4% had Grade 3 CRS. In the supportive safety analysis pool, 3.8% of LBCL patients and 4.0% of All B-NHL patients had Grade 3 CRS. One (0.3%) patient in the All B-NHL group had Grade 4 CRS and there were no Grade 5 CRS events. The difference in CRS incidence between the primary and supportive safety analysis pool was driven by the CRS rates reported in GCT3013-04 trial (>80%). The incidence of CRS was also higher in other diseases than DLBCL, i.e. iNHL and MCL (66.7%). Median time to CRS onset was 16 days (range 1-55) and correlated with the timing of the first full dose on C1D15. Almost all CRS event occurred during the first cycle. In study GCT3013-01, 6.6% had a CRS event at the priming dose, 12.9% at the intermediate dose, 43.6% at the first full dose, 4.6% at the second full dose, and 2.8% at the third full dose or after. No major differences in time to onset of CRS were observed across the different safety pools. The median time to CRS resolution in the primary safety analysis pool was 3.0 days (range: 1 to 27 days) and in the supportive safety analysis pool 3.0 days (range: 1 to 36 days). 46.1% received concomitant medication to treat CRS including 15.0% receiving tocilizumab and 10.8% receiving corticosteroids beyond prophylaxis. In 7.2% the dose was delayed and in 0.6% the event led to treatment discontinuation. In the supportive safety pool 01+04 All B-NHL, 56.4% received concomitant medication for CRS treatment and the proportion leading to treatment delay or discontinuation were comparable.

For the **event level analysis** (all CRS events are counted, including multiple episodes experience by the same individual patient) 123 events of CRS were reported in 84 patients in the primary safety analysis pool 01 LBCL. Among these 84 patients, 66.7% had 1, 23.8% 2, 7.1% 3, and 1.2% either 4 or 5 CRS episodes. No discernible risk factors for multiple CRS episodes could be identified. The supportive safety analysis pool showed similar numbers. The event level analysis did not provide new signals regarding grading, timing, and management of CRS.

ICANS- ICANS was reported in about 6.0% of patients in the primary and supportive safety analysis pools. Median time to onset correlated with the 1 to 2 days following the first full dose on C1D15. There were no Grade 3 or 4 ICANS events, but there was a Grade 5 ICANS event in the GCT3013-01 study. None of the other events led to treatment discontinuations and all other events resolved. Around 4% received concomitant medication to treat ICANS with dexamethasone, levetiracetam, and tocilizumab most commonly used.

CTLS- A total of 5 patients in the supportive safety analysis pool experienced CTLS, all treatment-related and in all patients the events were Grade 3 or 4.

Consistent with the MoA and also reported for medicinal products with the same target, e.g. mosunetuzumab, is the possible occurrence of **tumour flare** due to the influx of immune cells into tumour sites. In the epcoritamab safety pools, a total of 7 AEs with the PT tumour flare were observed,

leading to an overall rate of 1.9% (7/374). Overall, the events of epcoritamab were non serious, however, this might have been caused by the management guidance per protocol. Tumour flare is included in the SmPC as ADR in section 4.8 and as a warning in section 4.4 describing monitoring and management. An update of the analysis of AESIs (data cut-off date 30 June 2022) was similar to that seen in initial analysis for the primary safety analysis pool. In the supportive safety analysis pool, two new grade 4-5 CRS events and two new grade 4-5 ICANS events were reported following the first full dose of epcoritamab. However, according to the applicant, these high-grade events occurred in patients with very aggressive forms of MCL i.e., patients outside of the intended target population of the current application. Furthermore, these new CRS and ICANS events occurred within the first ≤8 week treatment period. Hence, the updated analysis confirms that the AESIs of CRS, ICANS and CTLS tend to occur during the first cycles of epcoritamab treatment.

In the pivotal GCT3013-01 study, 24-hours hospitalization was required following the first full dose of epcoritamab. However, the applicant has determined that hospitalization is not required in the post-approval setting to appropriately monitor for and manage the AESIs of CRS and ICANS. According to the applicant, most CRS events in the aNHL cohort (69/112 events 61.6%) occurred outside of the mandatory 24-hours hospitalization window in the GCT3013-01 study. However, this number is based on all CRS events occurring after any dose. Following the first full dose, the majority of events (43/68; 63.2%) occurred within the first 24 hours. The median time to onset of CRS after the first full dose was 20.6 hours and all (n=4) grade 3 CRS events occurred within the 24-hours hospitalization period after the first full dose. It is also noted in the updated pooled safety analysis (data cut-off date 30 Jun 2022) that two Grade 4 CRS events and one grade 5 (fatal) CRS event occurred in non-DLBCL patient population. To mitigate the risk of CRS after first full dose, the current SmPC includes a recommendation indicating patients should be hospitalised for 24 hours after administration of the Cycle 1 Day 15 dose of 48 mg to monitor for signs and symptoms of CRS and/or ICANS.

Other safety topics identified were Neurological events, cytopenia events, infections, and IRR.

Neurological events- Neurological events were analyzed with two approaches. The first approach used the method from the publication of Topp et al., 2015. The second method used a broad definition that included all TEAEs classified as SOC of nervous system disorders or psychiatric disorders, excluding sleep disorders and disturbances, and peripheral neuropathies. In the primary safety analysis pool, 25.7% experienced a neurological event per the Topp definition (10.2% related). Most commonly reported were ICANS, dizziness, paresthesia, and tremor. There were two Grade 3 events (facial paralysis, delirium), and two Grade 5 events (ICANS, loss of consciousness), of which the ICANS event was reported to be related. When using the broad definition, 35.3% experienced a neurological event (14.4% related). The proportions in the supportive safety analysis pools showed a similar pattern.

Cytopenia events- The incidence of neutropenia was around 10%-20% through the treatment period. The incidences of thrombocytopaenia and anaemia decreased to below 5% after Week 8. No patients discontinued treatment due to cytopenia. In the primary safety analysis pool, 28.1% had neutropenia and most events were Grade 3 or 4. In 15.0%, treatment with G-CSF was required. Febrile neutropenia occurred in 2.4%; all were Grade 3 or 4 and required treatment with G-CSF. A similar profile was observed in the supportive safety analysis pool.

Infections- In the primary safety analysis pool, 46.1% experienced an TEAE in the SOC Infections and infestations (8.4% related). In 14.4% the event was Grade 3 or 4 (1.2% related), and in 2.4% fatal (none related). Most commonly reported infections were urinary tract infection, COVID-19, oral candidiasis, upper respiratory tract infection, sepsis, and cellulitis. The incidence of infections was 26.9% during the Week ≤8 period, 6.7% during the Week 8 to ≤12 period, 28.8% during the Week 12 to ≤36

period, and 28.3% during the Week 36+ period. The supportive safety analysis pool did not reveal new signals with no major differences in incidences or type of infections. These data show that epcoritamab is associated with the occurrence of high grade and fatal events. An update on the occurrence of serious infections with data cut-off 30 June 2022 showed an increase compared to 31 January 2022. COVID-19 accounted for most of this increase. Although the intended patient population is known to be at risk of infections and none of the fatal infections was considered to be related to epcoritamab, a role of epcoritamab cannot be completely ruled out. In addition, bispecific antibodies are known to be associated with an increased infection risk. It will, therefore, be important to monitor for infections during treatment and to intervene early when identified. The applicant includes serious infection as important identified risk in the safety concerns, which is agreed.

IRR- Epcoritamab is administered per subcutaneous injection. In the primary safety analysis pool, 29.9% of patients reported IRR, all Grade 1 or 2. The incidence of IRR was highest during the Week ≤8 period, but occurred during all treatment periods. In 6.6%, patients had an IRR requiring treatment, generally consisting of topical steroids and/or oral antihistamines. None of the events resulted in dose modifications. The incidence of IRR was higher (40.1%) in the supportive safety analysis pool.

Serious adverse events- In the **primary safety analysis pool**, 58.1% reported a serious TEAE (36.5% related). Most serious TEAEs occurred in the first 8 weeks of treatment. Most common serious TEAEs were CRS, pleural effusion, febrile neutropaenia, ICANS, pneumonia, pyrexia, and sepsis. The **supportive safety analysis pool** showed a consistent profile.

Deaths- In the **primary safety analysis pool**, a **fatal TEAE** was reported in 7.2% (n=12) and a treatment-related fatal TEAE in 0.6% (n=1). The treatment-related fatal TEAE was caused by ICANS. Six of the fatal TEAEs were attributed to PD, three to COVID-19, and two to comorbidities/prior therapies, i.e. one case of progressive multifocal leukoencephalopathy to prior treatment with rituximab and one case of myocardial infarction with a medical history of multiple cardiovascular diseases. In the **supportive safety analysis pool**, fatal TEAEs were reported 5.1% (n=19). No fatal TEAEs were reported in the GCT3013-04 trial. Seven additional fatal TEAEs occurred in the All B-NHL group, and none were considered related. One additional fatal TEAE was attributed to PD, one to COVID-19, three to comorbidities/prior therapies (necrotizing fasciitis, lung opacity, pneumonia), and two to other reasons (septic shock, aspiration pneumonia). Especially for the fatal TEAEs in the SOC Infections and infestations a contributory role of epcoritamab cannot be ruled out completely. Concurrent cytopaenia was defined within 14 days prior to the infection event onset through the date of patients' deaths. Of the 9 patients, 6 experienced concurrent neutropenia or leukopenia (5 patients Grade 3-4) and 6 patients had concurrent lymphopenia (5 subjects Grade 3-4). Overall, of the 9 patients with a fatal infection, 8 had concurrent cytopaenias, in which 7 were Grade 3-4. The low number of cases make it difficult to draw conclusions, but *a contributory role of epcoritamab cannot be ruled out completely. As cytopaenias during epcoritamab treatment might cause an increased risk of infection, recommendations for management of febrile neutropaenia in the warning text for serious infections are included in the SmPC.*

Deaths occurring for any reason were reported in 40.7% in the **primary safety analysis pool**, mostly due to disease progression (32.3%). Other primary causes for death were adverse events (4.2%), other (3.6%), and unknown (0.6%). In the **supportive safety analysis pool** the number of deaths was lower (27.3%), mainly due to a lower proportion of deaths due to disease progression. It is agreed with the applicant that this is likely as a result of less time on study (enrollment ongoing) and less aggressive disease than LBCL.

Dose delays and discontinuations- No dose reductions for epcoritamab were allowed. In the **pivotal safety analysis pool**, 35.9% experienced an **TEAE leading to dose delay** (17.4% related). Most common TEAEs leading to dose delay were CRS, neutropaenia, pyrexia, acute kidney injury,

pleural effusion, and thrombocytopaenia. The **supportive safety analysis pool** showed a similar profile.

In the **pivotal safety analysis pool**, 7.8% **discontinued treatment due to an TEAE** (1.8% related). TEAEs leading to treatment discontinuation reported for more than 1 patient were COVID-19, COVID-19 pneumonia, and MDS in 2 (1.2%) patients each. Treatment-related TEAEs leading to treatment discontinuation included CRS, ICANS, and CLIPPERS (chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids) in 1 (0.6%) patient each, with the case of ICANS being fatal. Treatment-related TEAEs leading to treatment discontinuation in the **supportive safety analysis pool** included CRS in 2 (0.5%) patients; and ICANS, CLIPPERS, sepsis, enteritis, and multiple organ dysfunction syndrome in 1 (0.3%) patient each.

Immunological events- ADA analyses were not pooled for studies GCT3013-01 and GCT3013-04, because different assays were used to measure ADAs. In the All B-NHL group in study GCT3013-01, 8 patients (3.1%) were ADA positive on treatment, including 4 patients from the LBCL cohort and 4 patients from the iNHL or MCL cohorts. From the patients of the LBCL cohort with positive ADAs on treatment, none were positive at baseline, all had an onset of >C1D22 and 1 patient had a titer ≥1. No neutralizing antibodies were evaluated. Two patients discontinued the treatment within the first 2 cycles due to PD and the other two patients remained on treatment for >10 additional cycles. Three of the four patients experienced TEAEs that were not related to epcoritamab, and the other patient experienced treatment-related neutropaenia which resolved with continuing epcoritamab treatment. In study GCT3013-04, two patients were ADA positive on treatment and not at baseline. Both patients continued epcoritamab treatment. It is agreed with the applicant that overall, the incidence of ADAs to epcoritamab is low and a meaningful analysis of the impact of ADAs on safety is, therefore, limited, but no safety signals were observed. However, remaining uncertainties regarding immunogenicity of epcoritamab prevail due to unknown higher immunogenicity at lower dose, and the indeterminate category. ADA incidence in the target population DLBCL (3.1%) could potentially be higher than stated for the full 48 mg dose. The potential maximum incidence is still relatively low, and (based on the definition of the indeterminates), titres for these potential supplemental positive ADA patients are also relatively low (<1, 1:80). However, which titres that will provide neutralising effect are not known.

Laboratory findings- The most common **haematologic abnormalities** observed in the primary and supportive safety analysis pools were lymphopaenia followed by anaemia, thrombocytopaenia, and neutropaenia. The hematologic laboratory findings are expected for the MoA and disease to be treated.

Grade 3 or 4 **biochemistry** laboratory abnormalities were infrequent in all safety analysis pools. A total of 9 (2.4%) of 374 patients treated with epcoritamab in the supportive safety pool had **liver function tests** (LFT) elevations that met the first 2 laboratory criteria for potential drug-induced liver injury (DILI) according to Hy's law. The LFT elevations occurred in the context of CRS (5 patients), disease progression (3 patients), or cholangitis (1 patient). None of the cases is defined as DILI per the Hy's law criteria due to findings of cholestasis (ALP elevated >2x ULN) and/or another reason to explain increased ALT and total bilirubin.

Vital signs and ECG findings- The incidences of clinically notable vital sign abnormalities for the primary and supportive safety analysis pools were generally similar between pools, except for low systolic blood pressure and elevated temperature, which were more common in the supportive safety pool. In both safety pools, the most frequent abnormality was elevated temperature (>38°C). Overall, few patients (16 in the supportive safety pool, of which 9 were in the primary safety pool) experienced vital sign AEs that led to epcoritamab dose modification. No isolated vital sign AEs led to epcoritamab discontinuation. In the aNHL expansion cohort of study GCT3013-01, p*ostbaseline QTcF intervals >480-500 msec and >500 msec were reported in 4.3% and 3.2% (of which one also reported QTccf >500 ms at baseline), respectively. Of the 3 patients with QTcF >500 msec, 1 patient reported a TEAE*

of long QT syndrome, which was not considered related to epcoritamab. In 3.2% of patients with LBCL, a TEAE in the SOC of cardiac disorders was considered treatment-related, including 1.3% with tachycardia, 1.3% with sinus tachycardia, and 0.6% with sinus bradycardia. The supportive safety analysis pool, no new signals were observed. As is described in the non-clinical assessment, there were three sudden deaths in mice treated epcoritamab. Although the clinical relevance of this is difficult to determine, it could be caused by cardiac adverse events. However, the incidence of clinically significant ECG abnormality, QTcF >500 ms, and serious and Grade 3 or 4 TEAEs in the Cardiac disorders SOC is low. Combined with epcoritamab being a monoclonal antibody, no effect of epcoritamab on ΔQTcF in PK/PD analyses, and the profile of AEs in the SOC Cardiac disorders, there are no signals that epcoritamab has a clinically relevant effect on cardiac repolarization.

Subgroup results- Safety profiles were not affected by body weight or age.

The incidence of CRS was approximately 10-20% higher between subgroups in each category for female patients, Asian patients, patients treated in Asia, and in patients without prior CAR-T cell therapy. A higher incidence of CRS in patients with ≤3 prior lines of anti-lymphoma therapy compared to patients with >3 lines of anti-lymphoma therapy in the Safety Pool 01+04 All B-NHL seems to be largely driven by an increased incidence in the non-LBCL (i.e., non-target) population of the All B-NHL pool. The trends observed between subgroups may be confounded by several background variables (demographics, baseline disease characteristics and exposure data). In addition, the trends observed must be interpreted with caution due to uneven distribution of subjects in the different subgroups as well as a limited number of observations in certain categories (e.g., fatal TEAEs). A review of the pharmacokinetics of epcoritamab revealed no clinically meaningful differences between subgroups, and the trends observed for the safety profile in different subgroups do not appear to have had any clinically relevant impact on exposure to and efficacy of epcoritamab.

Patients with renal impairment (mild or moderate) or hepatic dysfunction (mild) at baseline, or who were Ann Arbor Stage III/IV showed trends towards higher frequencies of serious TEAEs and CRS, compared to patients with normal renal/hepatic function or who were Ann Arbor Stage I/II. However, the differences observed must be interpreted with caution due to the small sample size for some subgroups, and several *background demographic and disease variables might have confounded the results*. Epcoritamab was not studied in patients with severe renal impairment and severe hepatic impairment, and there was only 1 patient with moderately impaired hepatic function.

Only 8 patients in the GCT3013-01 expansion aNHL cohort had a CD20-negative tumour biopsy based on local assessment. The patients were considered to be CD20-positive for study inclusion based on documented evidence of CD20-positivity based on representative pathology. Due to the very limited number, it is difficult to draw any conclusions on the safety profile in CD20-negative patients compared to the overall populations, but there seem to be no safety signals in the CD20-negative patients.

As the sample sizes of the other disease entities than DLBCL NOS were very small, additional safety subgroup analyses for the different DLBCL disease entities will not be requested.

Safety data other ongoing studies with epcoritamab- High-level safety data were provided for studies GCT3013-02 and GCT3013-03. In study GCT3013-02 epcoritamab was administered in combination with other agents. In general, no new safety signals were identified, although the arm with GemOx seemed to be more toxic with 55.6% Grade ≥3 related TEAEs and 6 fatal TEAEs in 27 patients, of which 2 were related to epcoritamab and to GemOx. In study GCT3013-03 no new safety signals were identified based on the very limited data currently available. The incidence of CRS was very high (≥90% in both the escalation and the expansion phases), but this must be interpreted with caution given the small study population (n=12 CLL subjects in the escalation phase, and n=10 RS subjects in the expansion phase) and differences in baseline disease characteristics as compared to the

intended target population of the current application. It is agreed that no detailed safety information is provided for the GCT3013-05 trial, as it is an ongoing randomized study.

Adverse drug reactions- The applicant proposes to use the pool of the 167 LBCL patients from the GCT3013-01 study as basis for SmPC section 4.8. First of all, this pool of LBCL patients is representative for the intended DLBCL indication. Secondly, the applicant states that the combined safety pool with the GCT3013-04 study is not representative due to differences between the disease, patient population, and management between the GCT3013-01 and 04 studies. It is indeed agreed that the study GCT3013-04 differs from the -01 study, possibly due to the differences in study population and that this study does not have to be included in the SmPC safety information. The initial assessment of the ADRs by the applicant was re-evaluated upon request as it cannot be ruled out that epcoritamab played a contributory role in the development of certain events, especially given the MoA, the safety profile of similar products and the single arm trial design making it difficult to assess associations of adverse events and epcoritamab. Upon re-evaluation, events such as specific types of infections, tumour flare, fatigue, and biochemical abnormalities were added as ADRs. The applicant included oedema, musculoskeletal pain, abdominal pain, decreased appetite, and cardiac arrhythmias as ADR in the SmPC to resolve discrepancies. In addition, sodium decreased and creatinine increased are included in the ADR table in the SmPC.

GCP inspection- A routine GCP inspection has been performed for the escalation part of the GCT3013-01 study (EMA/IN/0000118168). Inconsistencies regarding the safety listings and the registration of AEs were identified related to SAEs, neurotoxicity events and two events of DLT were identified that are not listed in the CSR. The applicant has described the impact of the GCP findings and it is agreed that it seems that there may not be consequences for the B/R discussion. The applicant is requested to include the provision of the updated CSR of GCT3013-01-ESC CSR to be submitted on or before 22 Dec 2023 as part of an Annex II condition. The GCP inspection reported inconsistencies regarding the safety listings and the registration of AEs were identified related to SAEs, neurotoxicity events and at least two events of DLT were identified that are not listed in the CSR. Several (critical) deficiencies that were found could have had an impact on trial participants' rights and on the validity and integrity of the data. Currently the CSR is being updated and will be provided as a PAES (see Annex II). This update will include a summary of signal reports including neurotoxicity and in the DLT section, it will be noted that there were 2 events that met the criteria for DLTs but were not captured as DLTs because they did not occur in the dose-determining set. In addition, (S)AE listings will be adjusted to avoid misinterpretation on potential double entries.

The inspection has revealed inconsistencies in the safety reporting of the dose-finding study, as not all DLTs were reported and neurotoxicity events may have been inadequately captured. An update of the CSR was considered necessary by the inspectors, although it was concluded that the findings were unlikely to have significantly impacted data integrity. Regarding the GCP non-compliances, these are considered to be regrettable, however considered to be sufficiently addressed by the CAPAs.

Upon CHMP request, the applicant discussed the possible impact of the GCP findings in the escalation phase on DLT, neurotoxicity, potential double entries of CRS symptoms, and the CSR of the expansion phase.

- **DLT**: The first patient experienced hypersomnia at a higher intermediate dose than the intermediate dose as currently requested. The second patient experienced TLS following the intermediate dose at the dose selected as intermediate dose for the RP2D (0.8mg). Had this event been designated as a DLT, this would have been 1 DLT out of the total 25 subjects who had received 0.8 mg as the intermediate dose at that point in the study which was within the safety threshold. At this point it is difficult to conclude whether there was no impact of the 2 additional DLTs on selection of the epcoritamab RP2D or the conclusions in the GCT3013-01-

ESC CSR. However, as there is already an uncertainty identified whether the selected 0.16 mg/0.8 mg/48 mg proposed posology is the most optimal dose, this issue will not be further pursued at this point, but this might change when the updated CSR is assessed.

- **Neurotoxicity**: Because neurological toxicity AEs occurred at low frequencies and represented a developing safety signal, they were not discussed in detail in the general safety sections of the GCT3013-01-ESC CSR. However, these AEs were part of the source tables and listings and were considered in the study conclusions. Therefore, it is agreed with the applicant that there seems to be no impact of this finding on the conclusions of the GCT3013-01-ESC CSR.
- **Potential double entries of CRS symptoms**: The applicant has cross-checked the safety database and can confirm that no double-reporting of CRS symptoms to any Health Authority or EC/IRBs occurred. In the Marvin clinical database, the AESI of CRS was reported on a dedicated CRF form, with symptoms individually reported on an AE CRF to better characterize and understand the manifestations of the AESI. The GCT3013-01-ESC CSR SAE listing displayed the data as it was collected on the CRF pages. Because the symptoms had the "Is this AE serious" field ticked "Y, several of the signs and symptoms were included in the listing. Thus, it may have appeared that there was double-reporting on the listing, which was not the case.
- **CSR expansion phase**: It is agreed that the identified GCP findings are not likely to have an impact on the Expansion part of the GCT3013-01 study due to differences in the way that data were collected and reported. The design of the CRF was improved for the Expansion part of the study to prevent the appearance of double-reporting of AEs/symptoms in the listings and this should not be an issue for future CSRs. As clinical development of epcoritamab continued, additional data regarding neurological toxicity events and ICANS were captured in the Expansion part of the study. DLTs were not evaluated in the Expansion part of the study but changes have been made to the protocol template and CRF for collection of DLT data in future dose escalation studies.

With the provided explanations, it is agreed that the updated CSR of the escalation phase will be provided post-marketing. According to the applicant the following changes are expected:

- The applicant plans to discuss these additional 2 DLTs in Section 12.1 of the updated GCT3013-01-ESC CSR.
- The applicant will include a separate section that more thoroughly discusses any low-frequency neurological toxicity events in the SOCs of "nervous system disorders" and "psychiatric disorders" in the updated GCT3013-01-ESC CSR to be submitted on or before 22 Dec 2023.
- The applicant has updated the programming codes to ensure that the symptoms will be excluded from SAE Listing 16.2.7.3 in the updated GCT3013-01-ESC CSR that will be submitted on or before 22 Dec 2023.

Although the GCP findings had no impact on the Expansion part of the study, an updated GCT3013-01-EXP-aNHL CSR can also be provided upon request on or before 22 Dec 2023. It is not really understood, what type of updates are to be expected in the CSR of the expansion phase. The provision of the final CSR of the expansion phase is already part of the specific obligations and will be submitted in Q3/2026. Unless the updated CSR of the escalation phase warrants further updates of the CSR of the expansion phase, the submission of the final CSR of the expansion phase is considered sufficient.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

Additional safety data needed in the context of a conditional MA

To address the uncertainties of the absence of direct comparator data and a limited safety base in size and follow-up, the applicant proposes to provide additional data in the context of a CMA. Confirmatory data will be provided from the ongoing randomized controlled phase 3 trial GCT3013-05, comparing the efficacy and safety of epcoritamab to standard-of-care immunochemotherapy (i.e., R-GemOx or BR) in approximately 480 patients with R/R DLBCL. Additionally, the final CSR with longer follow-up of the ongoing GCT3013-01 will provide data to inform the long-term safety of epcoritamab in this patient population.

Regarding a MTA based on safety, it is agreed with the applicant that the different authorized medicinal products are characterized by specific safety profiles, but this does not automatically mean that the epcoritamab safety profile is beneficial compared to the other authorized products. More specifically, it is difficult to compare the tolerability of treatment and prevalence of specific adverse events in a meaningful way without any direct comparative studies.

With regards to the comparison to polatuzumab, the studies record substantially different rates of AEs associated with the particular mechanisms of action of polatuzumab and epcoritamab. Peripheral neuropathy is characteristic of tubulin targeting agents such as the vedotin toxin of polatuzumab, and was observed in 44% in polatuzumab + BR treated patients, whereas it was only reported in 2% of those treated with epcoritamab. Moreover CRS, which is characteristic of T-cell engagers, is seen in 49% of those treated with epcoritamab and not reported for polatuzumab + BR. Although it cannot be stated with certainty that one product is safer than the other, CRS is treatable and reversible, while neuropathy may be irreversible. Based on this, epcoritamab has a safety advantage over polatuzumab + BR due to the abovementioned differential ADR profiles resulting from the respective mechanisms of action.

Compared to the conditionally approved product loncastuximab tesirine, it is difficult to draw conclusions whether epcoritamab is associated with less severe toxicity, also taking into account the limitations of cross study comparisons. On the one hand, epcoritamab had numerically less Grade 3/4 AEs and AEs leading to discontinuation, but on the other hand more SAEs were reported. Fatal AEs were reported to a similar extent for epcoritamab and loncastuximab. The type of AEs observed for both products are different probably related to their different MoAs with specific toxicities of epcoritamab being CRS, ICANS, and serious infections; and oedema or effusion and increased liver function tests for loncastuximab tesirine, It can, therefore, not be concluded whether epcoritamab has a more favourable toxicity profile, but there are no signals that the toxicity profile is worse compared to loncastuximab tesirine. Furthermore, pixantrone is associated with cardiac failure, a known risk of anthracycline drugs and may be irreversible. Chemoimmunotherapy is associated with cytopaenias and gastrointestinal toxicity. Myelosuppression is observed for tafasitamab+lenalidomide. The type of AEs observed for CAR T cell therapies are similar to the ones reported for epcoritamab, but epcoritamab is immediately available.

2.6.10. Conclusions on the clinical safety

Overall, the safety profile is in line with what can be expected for a bispecific CD3/CD20-directed T-cell engager and the preclinical toxicity findings. Due to the MoA of activating T-cells CRS, ICANS, and CTLS are to be expected, as are cytopenias and infections with bispecific antibodies.

Important identified risks associated with epcoritamab therapy are CRS, ICANS, and (serious) infections.

The safety profile seems to be acceptable with monitoring and management guidelines considering the advanced nature of the disease and the pre-treated patient population under investigation.

Limitations of the safety database are that it is based on non-comparative data and on a limited sample size and follow-up time. The applicant proposes a CMA with confirmatory data from an ongoing randomized GCT3013-05 study with epcoritamab monotherapy. Longer follow-up of the GCT3013-01 study which is currently the basis for the safety profile will be provided with the final CSR of pivotal study GCT3013-01 as specific obligation.

The CHMP considers the following measures necessary to address the missing safety data in the context of a conditional MA:

- Evaluation of safety in long-term exposure (studies GCT3013-01, GCT3013-04, and GCT3013-05)
- Evaluation of overall safety profile with comparator data (study GCT3013-05)

2.7. Risk Management Plan

2.7.1. Safety concerns

Summary of safety concerns

Summary of safety concerns	
Important identified risks	CRS ICANS Serious infections
Important potential risks	Risk of overdose due to medication errors
Missing information	Long-term safety

2.7.2. Pharmacovigilance plan

On-going 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 3 of 2026

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 4 of 2024 Planned for Quarter 1 of 2029
Category 3 - Required additional PV activities				
Not Applicable				

2.7.3. Risk minimisation measures

Summary table of risk minimisation measures and pharmacovigilance activities

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 • 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

2.7.4. Conclusion

The CHMP considers that the risk management plan version 1.4 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did not request alignment of the PSUR cycle with the international birth date (IBD). The new EURD list entry will therefore use the EBD to determine the forthcoming Data Lock Points.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Labelling exemptions

A request to omit certain particulars from the labelling as per Art.63.1 of Directive 2001/83/EC has been submitted by the applicant and has been found acceptable by the QRD Group for the following reasons:

The QRD Group agreed on the proposed EN only vial label, as well as the 3-4 languages outer carton, provided all the legal multilingual requirements are met (e.g., for Belgium). The provision of an EN only package leaflet (inside the carton) could be acceptable as long as the MAH commits to print and distribute the national language package leaflets alongside the packs. A QR code could also be displayed on the carton directing to the package leaflet in all languages. Important information such as transport and storage conditions should be readily available on the outer carton and not displayed (hidden) on the extra flaps of the carton.

The particulars to be omitted as per the QRD Group decision described above will however be included in the Annexes published with the EPAR on EMA website, and translated in all languages but will appear in grey-shaded to show that they will not be included on the printed materials.

2.9.3. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Tepkinly (epcoritamab) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

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

3.1.2. Available therapies and unmet medical need

DLBCL patients after two or more lines of systemic therapy several therapies are available, namely:

- Chemo-immunotherapy (e.g. R-GemOX and BR); responses between 33%-66% have been observed, but these therapies are not associated with long term disease control/cure.
- CAR T-cell therapies directed at CD19, which have shown CR rates between 28% and 50% with generally long durations of response of >17 months, however these therapies do not have immediate availability.
- Polivy (anti-CD79b) plus BR for which a CR rate of 57%, an ORR of 70% and DoR of 10 months were observed.
- Minjuvi (monoclonal antibody against CD19) in combination with lenalidomide, an ORR of 57%, for which a CR rate of 40% and a DoR of 44 months were observed.
- Zynlonta (ADC targeting CD19); ORR is 48% with 25% of the patients in CR and a DoR of 10.3 months at a median FU of 7.8 months
- pixantrone (cytotoxic aza-anthracenedione) the ORR and CR rate at the end of the trial were 40% and 16%.

While approximately 50% of DLBCL patients are cured by first-line chemoimmunotherapy (Crump et al., 2017), outcomes are generally poor in patients for whom frontline treatment fails, in particular for primary refractory patients (Crump 2017). A recent study of R/R DLBCL patients indicated an ORR of 27.0% in the third line setting and 9.8% in the fourth- and later lines setting, with a median OS of only approximately 6 months in the third- or later lines setting (Radford, 2019). Further, there is lack of a consensus on SOC in the third and later lines setting. The majority of R/R DLBCL patients who have received two prior lines of systemic therapy are considered incurable.

The included aNHL disease entities constitute aggressive cancer types with poor prognoses and are considered seriously debilitating and life-threatening diseases. There is an unmet need in LBCL patients after two or more lines of systemic therapy to improve treatment outcomes in terms of increasing (duration of) CR, overcoming resistance to existing therapies and improving safety or providing a different safety profile compared to existing therapies. Treatment regimes used for HGBL and PMBCL, as well as for those with FL3b, overall are similar to those used for DLBCL and that there is a similar degree of unmet medical need across the disease entities included in the aNHL cohort. Also certain patients may need therapies with immediate availability (compared to CAR-T cells)

3.1.3. Main clinical studies

GCT3013-01 study is an ongoing FIH, phase 1/2, single arm trial in patients aged 18 years or older who had relapsed, progressive and/or refractory mature B-cell lymphoma including an escalation part and expansion part with aNHL cohort, an iNHL cohort and a MCL cohort. The expansion part of the aNHL cohort is presented as the pivotal study. In this cohort a study population of LBCL patients with relapsed or refractory (R/R) disease after at least 2 lines of systemic therapy were treated with epcoritamab monotherapy. As of the data cutoff date of 31 Jan 2022, a total of 157 subjects received at least one dose of epcoritamab monotherapy in the aNHL expansion cohort. In total 88.5% (N=139) DLBCL patients, 5.7% (N=9) HGBL patients, 2.5% (N=4) PMBCL patients and 3.2% (N=5) FL3B patients are included. In total 18 patients with HGBCL with *MYC* and *BCL2* and/or *BCL6* by either local or central analyses were included as part of the LBCL group. The median duration of follow-up was 10.7 months (range: 0.3, 17.9) and 11.0 months for the DLBCL group (range: 0.3, 17.9). Updated efficacy analyses from a data cut-off (DCO: 30 June 2022) with a median study duration follow-up of 15.7 months were provided in the response to the 1st RSI.

The epcoritamab dosing schedule in the aNHL expansion cohort consisted of a priming dose (0.16 mg), an intermediate dose (0.8mg) and subsequent full doses (48mg), administered subcutaneously QW in cycles 1-3, Q2W in cycles 4-9: and Q4W in cycles 10+.

The primary endpoint was ORR determined by IRC according to Lugano criteria, while important secondary endpoints included CRR, DOR, DOCR, TTR, OS, PFS and TTNT. The primary population for safety analyses includes 167 aNHL (LBCL) patients, of which 148 were DLBCL.

The escalation phase of the GCT3013-01 study was used for dose finding. The DLBCL cohort of the GCT3013-04 study in Japanese patients (N=36) and a real world evidence study are presented as supportive studies.

3.2. Favourable effects

The primary endpoint IRC-assessed ORR determined by Lugano criteria was 63.1% (95% CI: 55.0, 70.6) in LBCL patients with 38.9% (95%CI: 31.2, 46.9) of the patients in CR.

The median DOR by Lugano criteria as assessed by IRC was 12.0 months (95% CI: 6.6, NR) and the median DOCR was 12.0 months (95% CI: 9.7, NR) in LBCL patients. The median TTR (by IRC) was 1.4 (range: 1.0, 8.4) months in LBCL patients, median TTCR was 2.7 months (range: 1.2, 11.1).

Subgroup analyses are generally consistent with the primary analysis, but indicate better responses in subgroups related to longer time since prior anti CD20 therapy.

In the DLBCL patients the ORR was 61.9% (95%CI: 53.3, 70.0) and the CR rate 38.8% (95%CI: 30.7, 47.5). The median DOR, DOCR, TTR, and TTCR in the DLBCL subgroup are the same as in LBCL patients. In the other LBCL entities responses were seen in all four FL3B (3 patients in CR), in all five PMBCL patients (2 patients in CR) and in 44% (N=4/9) HGBL patients (2 patients in CR).

The median PFS was 4.4 months (95% CI: 3.0, 8.2) in both the DLBCL and LBCL groups. The median OS was not reached (95% CI: 11.3, NR) in both the DLBCL group (56 events) and LBCL group (61 events).

Updated efficacy analyses from a data cut-off (DCO: 30 June 2022) indicate similar response rates compared to the primary analyses. The updated median DOR in subjects with LBCL is 15.5 (9.7, NR) months and in DLBCL patients 15.6 months (95% CI: 9.7, NR).

In the GCT3013-04 study in a similar population of Japanese patients, the ORR based on IRC assessment by Lugano criteria was 55.6% (95% CI: 38.1, 72.1) with a CR rate of 44.4% (95% CI: 27.9, 61.9) and the median DOR was not reached at a median follow up of 8.4 months

3.3. Uncertainties and limitations about favourable effects

The pivotal study is a single arm, exploratory study. This study design introduces inherent limitations as the therapeutic effect might be subject to various sources of bias. In addition, efficacy may be overestimated in such a study design. Therefore, the results should be interpreted with caution, however it should also be noted that replication is observed in an independent GCT3013-04 study, which diminishes the concerns on chance findings.

The uncontrolled nature of the pivotal study GCT3013-01 means that the treatment effect on time-to-event outcomes such as PFS and OS cannot be truly isolated, and therefore these results should be interpreted with caution.

The choice of 0.16 mg/0.8 mg/48 mg as proposed posology is not objected, however it is uncertain whether the most optimal dose has been selected. Exposure-response analyses support the 48 mg as a dose with acceptable efficacy and safety, but also indicates that other doses might be equally effective/safe. Furthermore, there seems to be some data pointing to a rationale for a type of step up dosing, however this is not directly confirmed or sufficiently supported with non-clinical or clinical data.

The usefulness of the real-world data is very uncertain considering the methods which led to differences in the pivotal study population and the real world study population. A prolonged patient inclusion period during which new therapies and new response criteria where introduced, limit the usefulness of the real world data for contextualization purposes.

3.4. Unfavourable effects

The primary safety analysis set included 167 patients with LBCL, including 148 DLBCL patients, from the dose escalation and expansion parts of the GCT3013-01 study who were assigned to receive the 48 mg full dose of epcoritamab and received at least 1 dose of epcoritamab. Data cutoff date for the safety analysis was at 31 January 2022.

- Median treatment duration was 3.7 months with 69 patients (41.3%) having at treatment duration of 6 months and 30 patients (18.0%) having a treatment duration of ~12 months. At data cutoff, 31.7% were still on study treatment.
- The most common (≥20%) TEAEs of any grade included CRS (50.3%), fatigue (24.6%), pyrexia (22.8%), injection site reaction (22.2%), neutropaenia (22.2%), and nausea (20.4%). Most events occurred in the first 8-week treatment period.
- Most TEAEs were Grade 1 or 2 in severity (except for cytopaenias), and most events occurred with highest frequency during the first 8 weeks of treatment (except for infections with similar incidences in the different treatment periods).
- Based on investigator assessment, treatment-related TEAEs reported in ≥10% of patients included CRS (50.3%), injection site reactions (22.2%), neutropaenia (18.0%), fatigue (15.0%), and pyrexia (11.4%). Apart from neutropaenia, most treatment-related TEAEs were low-grade.
- Grade 3 or higher TEAEs were reported in 62.9%. The most common (≥5%) Grade 3 or 4 TEAEs were haematological and included neutropenia (15.6%), anaemia (10.2%), neutrophil count decreased (6.0%), and thrombocytopaenia (6.0%).

- Serious TEAEs were observed in 58.1%. The most common serious TEAEs (≥2%) included CRS (31.1%), pleural effusion (4.8%), pneumonia (2.4%), febrile neutropaenia (2.4%), pyrexia (2.4%), sepsis (2.4%), and ICANS (2.4%).
- Fatal (Grade 5) TEAEs were reported in 12 (7.2%) patients, of which one event of ICANS was considered to be related to epcoritamab. The other fatal TEAEs were considered to be related to disease progression, COVID-19, or existing comorbidities/impact of prior therapies.
- TEAEs leading to treatment discontinuation was seen in 7.8%, most often due to myelodysplastic syndrome, COVID-19, and COVID-19 pneumonia.
- CRS, ICANS, and CTLS were considered to be AESI, consistent with the mechanism of action of epcoritamab.
    - CRS was experienced by 50.3%, with 31.1% having maximum Grade 1, 16.8% maximum Grade 2, and 2.4% maximum Grade 3. Most events occurred with the first full dose. The median time to resolution of CRS events was 2.0 days. 46.1% received concomitant medication to treat CRS including 15.0% receiving tocilizumab and 10.8% receiving corticosteroids beyond prophylaxis. In 0.6% the event led to treatment discontinuation.
    - ICANS occurred in 6.0%, with 4.2% having maximum Grade 1, 1.2% maximum Grade 2, and 0.6% Grade 5 ICANS. The median time to resolution was 5.0 days and none of the events led to treatment discontinuation.
    - CTLS was reported in 1.2%, all were Grade 3 or higher and were unresolved when the patients died of disease progression.
- Serious TEAEs of infection were reported in 16.2% and fatal infections in 2.4%; none of the fatal infections were considered related to epcoritamab.

A larger supportive safety analysis set consisted of patients from both the GCT3013-01 and the GCT3013-04 studies who were assigned to receive the 48 mg dose regimen and received at least 1 dose of epcoritamab with 374 patients with B-NHL. The safety results from the supportive safety analysis set were generally consistent with the primary safety analysis set of patients with LBCL, although the incidence of CRS was higher in the supportive safety pool. Uncertainties and limitations about unfavourable effects

3.5. Effects Table

Table 75: Effects Table for epcoritamab in with relapsed or refractory disease after at least 2 lines of systemic therapy (data cut-off: 30 June 2022) – expansion part of the GCT3013-01 study.

Effect	Short Description	Unit	Treatment	Uncertainties/ Strength of evidence	References
ORR	Overall response rate LBCL DLBCL	 N (%) 95%CI	 99 (63.1%) 55.0, 70.6 86 (61.9%) 53.3, 70.0	Single arm trial, exploratory study. Indication sought in the subgroup of DLBCL (NOS) patients. Support from other secondary endpoints and study GCT3013-04. Uncertain whether	Study GCT3013-01

				the most optimal dose has been selected.	
CR	Complete response rate LBCL DLBCL	 N (%) 95%CI	 61 (38.9%) 31.2, 46.9 54 (38.8%) 30.7. 47.5	Idem.	
DoR	Median duration of response LBCL DLBCL	 months 95%CI	 15.5 9.7, NR 15.6 9.7, NR	Idem. Short median follow up.	
DoCR	Median duration of complete response LBCL DLBCL	 Months 95%CI	 NR 14.3, NR NR 14.3, NR	Idem.	
Grade ≥3 TEAEs	LBCL pool 01 All B-NHL pool 01+04	%	65.9 68.7	Based on single arm studies with no comparator. Safety database is limited in size and follow-up.	CSRs, summary of clinical safety
Serious TEAEs	LBCL pool 01 All B-NHL pool 01+04		64.1 63.1		
Fatal TEAEs	LBCL pool 01 All B-NHL pool 01+04		8.4 7.4		
TEAEs leading to discontinuations	LBCL pool 01 All B-NHL pool 01+04		10.2 9.3		
CRS	LBCL pool 01 All B-NHL pool 01+04		50.9 62.9		
ICANS	LBCL pool 01 All B-NHL pool 01+04		6.0 6.5		
CTLS	LBCL pool 01 All B-NHL pool 01+04		1.8 1.6		
Serious infections	LBCL pool 01		24.6		

	All B-NHL pool 01+04		26.5		

Abbreviations: CI= confidence interval, CRS= cytokine release syndrome, CTLS= clinical tumor lysis syndrome, ICANS= immune effector cell-associated neurotoxicity syndrome, number, NR= not reached, TEAE= treatment-emergent adverse event.

3.6. Benefit-risk assessment and discussion

3.6.1. Importance of favourable and unfavourable effects

The prognosis for patients with R/R DLBCL remains poor and new treatment alternatives in this setting are welcome. Therefore, the responses and duration of response observed in the study population of aNHL subtype DLBCL, who are R/R after two or more lines of systemic therapy are considered to be clinically relevant. Particularly the CR rate associated with epcoritamab is considered to be of relevance for patients. The response occurs shortly after treatment initiation, which is considered important in a population with rapidly progressing disease. Of note, clinically relevant results have also been observed in HGBL and DH/TH disease, PMBCL and FL3B. Although subgroups are small, based on the MoA of epcoritamab and similarities in disease and biology to DLBCL, benefit could also be expected in these patients.

The single arm, exploratory design of the study, however, introduces inherent limitations as the observed therapeutic effect might be subject to various sources of bias. In addition, efficacy may be overestimated in such a study design, the sample size is limited, duration of follow-up is short and there is possible variability in treatment efficacy across the population included. Therefore, the results should be interpreted with caution and confirmation of efficacy in the target patient population is required. As such the request for conditional approval is appropriate, meeting the requirements for a conditional approval is discussed below.

Overall, the safety profile is in line with what can be expected for a bispecific CD3/CD20-directed T-cell engager and the preclinical toxicity findings with CRS, ICANS, CTLS, cytopaenias, and infections. Limitations of the safety database relate to the data being of non-comparative nature and the limited sample size and follow-up time, although there is clinical experience with other bispecific T-cell engagers. The safety profile seems to be acceptable with monitoring and management guidelines considering the advanced nature of the disease and the pre-treated patient population under investigation.

3.6.2. Balance of benefits and risks

Clinically relevant (complete) responses and duration of response were observed in DLBCL patients who are R/R after two or more lines of systemic therapy. The benefit is considered to outweigh the safety profile. However, confirmation of efficacy and safety is needed due to the limitations associated with the study design (see section 3.7.3. below).

3.6.3. Additional considerations on the benefit-risk balance

As discussed, the single arm exploratory trial design introduces inherent limitations in the interpretation of the results, based on non-comparative data, further the safety database is limited in size and follow-up. Overall, the results of the pivotal study should be interpreted with caution and confirmation of efficacy and safety in the R/R DLBCL population is required. Although it should be

noted that replication is observed in GCT3013-04 study, which diminishes the concerns on chance findings.

Based on the above, the clinical data cannot be considered comprehensive.

Conditional Marketing Authorisation

As comprehensive data on the product are not available as discussed above, a conditional marketing authorisation was requested by the applicant in the initial submission.

The product falls within the scope of Article 14-a of Regulation (EC) No 726/2004 concerning conditional marketing authorisations, as it aims at the treatment of a seriously debilitating, life-threatening disease. In addition the product is designated as an orphan medicinal product.

Furthermore, the CHMP considers that the product fulfils the requirements for a conditional marketing authorisation:

- **The benefit-risk balance is positive**

The benefit – risk balance is positive (see section 3.6.)

- **It is likely that the applicant will be able to provide comprehensive data.**

Phase 3 GCT3013-05 is proposed as a confirmatory study. This study is an open-label, randomised, trial of epcoritamab versus the pre-specified investigator's choice of SOC of R-GemOx or BR in patients aged 18 years or older with R/R DLBCL who failed a previous ASCT or are ineligible for ASCT at screening and previously treated with at least 1 line of systemic antineoplastic therapy, including anti-CD20 monoclonal antibody-containing combination chemotherapy. Approximately 480 subjects with DLBCL and HGBL (240 in each arm) will be enrolled in the trial, with a primary endpoint of OS. In order to confirm the safety and efficacy of epcoritamab in the treatment of R/R DLBCL after two or more lines of systemic therapy, the results of the primary and final safety and efficacy analyses for study GCT3013-05 should be submitted. The proposed due date for the primary analysis CSR (including final OS analysis) is Q4/2024. The proposed due date for the final CSR including long term safety data is Q1 2029.

The applicant agrees to submit the final CSR for the pivotal GCT30313-01 study as specific obligation.

- **The unmet medical need will be addressed**.

When comparing the efficacy results of epcoritamab to available therapies for the target population with a CMA, being Minjuvi, Zynlonta and Columvi, epcoritamab addresses the unmet medical need to a similar extent with no signals that the toxicity profile of epcoritamab is worse compared to Minjuvi Zynlonta and Columvi. The applicant has satisfactorily provided evidence of MTA over polatuzumab vedotin (+BR), CAR-T therapies and pixantrone which have a full MA.

Compared to therapies with a full approval, epcoritamab has numerically substantial higher rates in terms of ORR and CR rate compared to Pixuvri, which together with the long DoR epcoritamab for epcoritamab will provide meaningful clinically effects for the target population. It is also noted that many (D)LBCL patients in 3L+ will have met their maximum recommended anthracycline allotment and therefore further treatment with anthracycline drugs (such as Pixuvri) will come with a risk of precipitating heart failure, whereas this risk is not expected with epcoritamab.

With regards to CAR T cells (Kymriah, Yescarta and Breyanzi), it is noted that ORR and CR rate are numerically lower compared to Yescarta, Breyanzi. However, it is considered that epcoritamab introduces a MTA in patient care over all CAR T-cell therapies (Kymriah, Yescarta and Bryeanzi) epcoritamab will present a treatment for immediate administration to the patient.

With regard to Polivy+ BR potential differences in analysis methods and the inherent weaknesses of cross study comparisons do not allow firm conclusions of MTA in terms of ORR and CR rate; when considering the median DOR cross-study comparison seems to favor epcoritamab over polatuzumab + BR.

Nonetheless , it is considered that epcoritamab will provide meaningful clinical effects in patients with R/R DLBCL, particularly as evidence of activity is shown in patients who have failed prior CAR t cell therapy. Thus constitute an additional treatment option in this non-curative 3L+ setting. Regarding the safety profile, it is difficult to compare the tolerability of treatment and prevalence of specific adverse events in polatuzumab +BR treated compared to epcoritamab treated cohorts in a meaningful way without any direct comparative studies. However, the studies record substantially different rates of AEs associated with the particular mechanisms of action of polatuzumab and epcoritamab. Peripheral neuropathy is characteristic of tubulin targeting agents such as the vedotin toxin of polatuzumab, and was observed in 44% in polatuzumab + BR treated patients, whereas it was only reported in 2% of those treated with epcoritamab. Moreover CRS, which is characteristic of T-cell engagers, is seen in 49% of those treated with epcoritamab and not reported for polatuzumab + BR. Although it cannot be stated with certainty that one product is safer than the other, CRS is treatable and reversible, while neuropathy may be irreversible. Based on this, epcoritamab has a safety advantage over polatuzumab + BR due to the above mentioned differential ADR profiles resulting from the respective mechanisms of action.

A MTA of epcoritamab over polatuzumab + BR has been shown based on the lack of peripheral neuropathies. Additionally, compared to polatuzumab + BR, epcoritamab has shown evidence of activity in patients who have failed prior CAR t cell therapy, while polatuzumab + BR has yet to demonstrate effect in this setting.

The route of administration as subcutaneous (SC) has been discussed in terms of patient convenience, however it is uncertain if this led to advantages for patients such as decreased hospitalisation, and reduced treatment burden and does not constitute a MTA.

In conclusion, an MTA has been shown for epcoritamab over approved products (Kymriah, Yescarta, Breyanzi, Polivy, Pixruvi) and epcoritamab addresses the unmet medical need to at least a similar extent as the conditionally approved products (Minjuvi, Zynlonta and Columvi).

- **The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required.**

Given the aggressiveness of the disease and poor prognosis in R/R DLBCL patients in the third- and later lines of therapy, as well as the fact that the benefit-risk balance of Tepkinly is positive (see assessment above), it is agreed that the benefits to public health of immediate availability outweigh the risks inherent in the fact that additional data are still required.

3.7. Conclusions

The overall benefit/risk balance of Tepkinly is positive, subject to the conditions stated in the section 'Recommendations'.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Tepkinly is not similar to Yescarta, Polivy, Minjuvi,

Kymriah and Columvi within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Tepkinly is favourable in the following indication:

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

The CHMP therefore recommends the granting of the conditional marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

  Additional risk minimisation measures to minimise 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 Marketing Authorisation Holder (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

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	**Due date**
Post-authorisation efficacy study (PAES) Submission of the updated CSR of GCT3013-01-ESC	Q4 2023

Specific Obligation to complete post-authorisation measures for the conditional marketing authorisation

This being a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	**Due date**
In order to confirm the safety and efficacy of epcoritamab in the treatment of R/R DLBCL after two or more lines of systemic therapy, the primary (including final OS analysis) and final CSR for study GCT3013-05 should be submitted. - Primary analysis CSR (including final OS analysis) - Final CSR	Q4/2024 Q1/2029
In order to confirm the safety and efficacy of epcoritamab in the treatment of relapsed or refractory DLBCL after two or more lines of systemic therapy, the MAH should submit the final CSR for the pivotal aNHL cohort of study GCT3013-01.	Q3/2026

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

These conditions fully reflect the advice received from the PRAC.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that epcoritamab is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.