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Committee for Medicinal Products for Human Use (CHMP)

Extension of indication variation assessment report

Tepkinly

International non-proprietary name: Epcoritamab

Procedure No. EMEA/H/C/005985/II/0001

Note

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

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List of abbreviations

ADA	anti-drug antibody (ie, anti-epcoritamab antibody)
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AML	acute myeloid leukemia
aNHL	aggressive B-cell non-Hodgkin lymphoma
ASCT	autologous stem cell transplantation
AST	aspartate aminotransferase
ASTCT	American Society for Transplantation and Cellular Therapy
ATC	anatomical therapeutic chemical
AUC	area under the concentration-time curve
$AUC_{0-\infty}$	area under the curve from time zero extrapolated to infinity
AUC_{0-last}	area under the curve from time zero to the last measurable concentration
BOR	best overall response
CAR T-cell	chimeric antigen receptor T-cell
CARTOX-10	CAR T-cell-therapy-associated toxicity 10-point neurological assessment
CI	confidence interval
C_{max}	maximum concentration
CNS	central nervous system
COVID-19	coronavirus disease - 2019
CR	complete response
CRF	case report form
CRO	contract research organization
CRS	cytokine release syndrome
CSR	clinical study report
CT	computed tomography
CTLS	clinical tumor lysis syndrome
CV	coefficient of variation
CxDx	Cycle x Day x
DCO	data cutoff
DDS	Dose-determining Set
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
DMC	Data Monitoring Committee
DOCR	duration of complete response
DOR	duration of response
ECG	electrocardiogram
ECLIA	electrochemiluminescence immunoassay
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
eTMF	electronic trial master file

EU	European Union
FAS	Full Analysis Set
FcRn	Fc receptor (neonatal)
FDA	Food and Drug Administration
FIH	first-in-human

FL	follicular lymphoma
GCP	Good Clinical Practice
HDT	high-dose therapy
HLT	high-level term
HSCT	hematopoietic stem cell transplantation
IAS	Immunogenicity Analysis Set
ICANS	immune effector cell-associated neurotoxicity syndrome
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IFN	interferon
Ig	immunoglobulin
IL	interleukin
iNHL	indolent B-cell non-Hodgkin lymphoma
INR	international normalized ratio
IRB	Independent Review Board
IV	intravenous(ly)
LBCL	large B-cell lymphoma
mAb	monoclonal antibody
MABEL	minimum anticipated biologic effect level
mBOIN	modified Bayesian optimal interval
MCL	mantle cell lymphoma
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
MTD	maximum tolerated dose
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NHL	non-Hodgkin lymphoma
NR	not reached
ORR	overall response rate
OS	overall survival
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic(s)
PMBCL	primary mediastinal B-cell lymphoma
PR	partial response
PT	preferred term
Q2W	once every 2 weeks
Q4W	once every 4 weeks
QTcB	corrected QT interval (Bazett's formula)
QTcF	corrected QT interval (Fridericia's formula)

QTL	quality tolerance limit
QW	once weekly
RES	Response Evaluable Set
RNA	ribonucleic acid
RP2D	recommended phase 2 dose
R/R	relapsed or refractory

SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous(ly)
SCT	stem cell transplant
SMCIA	single molecule counting immunoassay
SOC	system organ class
SPD	sum of the product of the diameters
SSC	Sponsor Safety Committee
$t_{1/2}$	half-life
TEAE	treatment-emergent adverse event
TLS	tumor lysis syndrome
T_{max}	time to reach C_{max}
TNF	tumor necrosis factor
TTNT	time to next (anti-lymphoma) therapy
UK	United Kingdom
ULN	upper limit of normal
US	United States
WHO	World Health Organization

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, AbbVie Deutschland GmbH & Co. KG submitted to the European Medicines Agency on 7 November 2023 an application for a variation.

The following variation was requested:

Variation requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, IIIA, IIIB and A

Extension of indication to include treatment of adult patients with relapsed or refractory (R/R) follicular lymphoma (FL) after two or more lines of systemic therapy for TEPKINLY, based on results from the indolent Non-Hodgkins Lymphoma (iNHL) expansion cohort of Study GCT3013-01, the First In Human (FIH) Phase 1/2 study in R/R B-NHL, and key supportive data from the Phase 1b/2 Study GCT3013-04 in Japanese subjects. Study GCT3013-01 is an ongoing global, single-arm, Phase 1/2 study designed to evaluate epcoritamab as monotherapy in R/R B-NHL. As a consequence, sections 1, 3, 4.1, 4.2, 4.4, 4.8, 5.1, 5.2, 6.3, 6.4, 6.5 and 6.6 of the SmPC are updated. The package leaflet and labelling are updated in accordance. Version 2.0 of the RMP has also been submitted. In addition, the MAH took the opportunity to introduce minor changes to the product information (PI).

The variation requested amendments to the Summary of Product Characteristics, Labelling, Package Leaflet and Annex A and to the Risk Management Plan (RMP).

Information relating to orphan designation

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

Tepkinly was also designated as an orphan medicinal product EU/3/22/2634 on 21 June 2022 for the treatment of follicular lymphoma.

Following the CHMP positive opinion on this marketing authorisation and at the time of the review of the orphan designation by the Committee for Orphan Medicinal Products (COMP), this product was withdrawn from the Community Register of designated orphan medicinal products on 19 July 2024 on request of the sponsor. The relevant orphan designation withdrawal assessment report can be found under the 'Assessment history' tab on the Agency's website www.ema.europa.eu/en/medicines/human/EPAR/Tepkinly

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.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision P/0415/2022 on the agreement of a paediatric investigation plan (PIP) (EMEA-002907-PIP01-20) and the granting of a (product-specific) waiver applying to the paediatric population from birth to less than

1 year of age on the ground that the disease or condition for which the specific medicinal product is intended does not occur in the specified paediatric subset.

At the time of submission of the application, the PIP EMEA-002907-PIP01-20 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

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

MAH request for additional market protection

The MAH requested consideration of its application in accordance with Article 14(11) of Regulation (EC) 726/2004 - one year of market protection for a new indication.

In order to address this request, a separate CHMP AR is included as an appendix to this report.

Scientific Advice

The MAH received Protocol assistance from the CHMP on 25 June 2020 (EMEA/H/SA/4478/1/2020/III) and 15 Oct 2020 (EMEA/H/SA/4478/2020/I). The Scientific Advice pertained to the following quality, non-clinical and clinical aspects:

- 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 FL;
- Design of the aNHL expansion cohort of the ongoing Phase 1/2 Trial GCT3013-01 to support 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;
- whether the GCT3013-TBD trial of epcoritamab+ rituximab and lenalidomide (R2) versus R2 alone may serve as the confirmatory trial under a specific obligation if a CMA is granted for this indication;
- 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;

At 15 September 2022 the MAH received Scientific Advice (EMEA/SA/0000095173) on the following Clinical aspects;

- Revised design of the Phase 3 Study M20-638 of epcoritamab in combination with rituximab and lenalidomide (R2) in subjects with relapsed/refractory FL, in particular choice of patient population, comparator and planned treatment arms, secondary endpoints, statistical analysis plan, PRO measurement strategy and pharmacokinetics sampling plan

- Proposed initiation of the pivotal trial with investigational arms for 2 different doses of epcoritamab concurrently with planned dose optimization studies

- Acceptability of proposed data package from the iNHL expansion cohort of the Phase 1/2 Study GCT3013-01 to support a conditional marketing authorisation of epcoritamab monotherapy in relapsed/refractory follicular lymphoma and of phase 3 Study M20-638 to serve as the confirmatory trial.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Peter Mol Co-Rapporteur: Ingrid Wang

Timetable	Actual dates
Submission date	7 November 2023
Start of procedure:	25 November 2023
CHMP Rapporteur Assessment Report	19 January 2024
PRAC Rapporteur Assessment Report	26 January 2024
PRAC members comments	31 January 2024
CHMP Co-Rapporteur Assessment	31 January 2024
PRAC Outcome	8 February 2024
CHMP members comments	12 February 2024
Updated CHMP Rapporteur(s) (Joint) Assessment Report	15 February 2024
Request for supplementary information (RSI)	22 February 2024
CHMP Rapporteur Assessment Report	6 May 2024
PRAC Rapporteur Assessment Report	6 May 2024
PRAC members comments	7 May 2024
PRAC Outcome	16 May 2024
CHMP members comments	17 May 2024
Updated CHMP Rapporteur Assessment Report	23 May 2024
Request for supplementary information (RSI)	30 May 2024
CHMP Rapporteur Assessment Report	12 June 2024
CHMP members comments	17 June 2024
PRAC members comments	17 June 2024
Updated PRAC Rapporteur Assessment Report	20 June 2024
Updated CHMP Rapporteur Assessment Report	20 June 2024
Opinion	27 June 2024

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

The claimed new therapeutic indication is:

- as monotherapy for the treatment of adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy.

Epidemiology and risk factors, screening tools/prevention

Follicular lymphoma (FL) is the second most prevalent type of NHL, representing 25% of NHL cases, and is the most common type of iNHL (Swerdlow, 2008). With this incurable malignancy exhibits a high degree of clinical heterogeneity, ranging from an indolent to a highly aggressive clinical course. After each successive line of therapy, patients with relapsed or refractory (R/R) disease experience significantly decreased response rates, shortened duration of response (DOR), and a higher mortality rate (Revas-Delgado, 2019; Casulo, 2015; Link, 2019).

The median age at diagnosis of FL is 65 years.

Autoimmune disease and some occupational exposures have been identified as risk factors of FL.

Biologic features

Malignant lymphoma represents a disease entity characterized by malignant transformation of the cells from lymphoid tissue. Approximately 90% of lymphomas in Western countries are of B-cell origin (NL-Classification Project, 1997). NHLs comprise a heterogenous group of malignancies that arise from haematopoietic progenitor cells. The majority of B-cell lymphomas express B-cell markers, such as CD19, CD20, CD22, and CD79b (Swerdlow, 2016). Clinically, B-cell non-Hodgkin lymphoma (NHL) has been divided into aggressive non-Hodgkin lymphoma (aNHL) and indolent non-Hodgkin lymphoma (iNHL), which is generally more slow-growing.

B cell NHLs arise from B-lymphocytes and have the cell surface characteristics of normal B-cell differentiation. FL tumour cells are considered to be malignant counterparts of normal germinal center B cells in the lymph nodes. Morphologically, the malignant B-cells typically forms a follicular growth pattern.

The current WHO edition defines FL in accordance to number of centroblastic cells as Grade 1, Grade 2, Grade 3A and Grade 3B. The distinction between Grade 3A and 3B is important due to their apparent differences in molecular genetics and prognosis; it is suggested that Grade 3A FL (no centrocytes, centroblasts only) is on the same spectrum as Grade 1-2 FL, and Grade 3B FL behaves as de novo DLBCL (Katzenberger , 2004; Karube, 2007).

As in the majority of other mature B-cell lymphomas, FL is characterized by the expression of a surface membrane antigen, CD20. CD20 is an attractive target for anti-lymphoma therapies, being B-cell-specific, highly and stably expressed, exhibiting a low rate of internalization, and not being present on hematopoietic stem cells. The concept of targeting CD20 as an effective anti-lymphoma strategy has been validated by clinical data for the anti-CD20 monoclonal antibody rituximab, which has revolutionized the treatment of FL. The utility of CD20 as a therapeutic target has led to the continued development of improved anti-CD20 monoclonal antibodies.

Clinical presentation, diagnosis and stage/prognosis

Patients typically present with asymptomatic lymphadenopathy; however, the majority of patients are diagnosed with advanced disease (Ann Arbor Stage III/IV). Patients with advanced FL are not cured with available conventional therapies. The 5-year survival rate is approximately 90% and 10-year survival is around 75% (Sarkozy, 2019).

Clinical behaviour of FL is variable, ranging from an indolent course over decades to a clinically more aggressive course with increasing refractoriness and decreasing duration of response to therapy.

The FLIPI is the most widely used prognostic scoring system to predict survival in newly diagnosed patients, dependent on identified clinical risk factors (age > 60 years, stage III-IV, hemoglobin < 120 g/L, number of nodal areas > 4, and serum LDH level above normal).

Beyond the front-line setting, prognosis is influenced by several factors, including number of prior regimens, refractory status, and progressive decline of bone marrow reserve (Smith, 2013).

A relatively high risk of death is observed in patients with early progression of disease, specifically within 24 months of commencing first-line immunochemotherapy (Casulo, 2017, Seymour, 2019).

It is reported that for patient receiving a second course of rituximab-containing chemotherapy at the time of first relapse, achieving a CR or receiving autologous hematopoietic stem cell transplantation in the second-line setting is associated with improved PFS (time to second disease progression) (Liu, 2020).

In patients who progress from front-line therapies, the disease-free intervals and DOR become progressively shorter with increased refractoriness with each subsequent progression/relapse (Link, 2019; Rivas-Delgado, 2019). Patients with R/R FL after ≥2 prior lines of therapy are a particularly poor prognostic group. Median PFS ranging from 1 to 1.1 years for third-line patients decreasing to 0.5 years for sixth-line patients with a corresponding median OS of 4.8 to 8.8 years and 1.9 years, respectively (Alperovich, 2016, Batlevi, 2020, Rivas-Delgado, 2019).

A real-world analysis of patients with R/R FL receiving systemic therapy after ≥2 prior therapies (including an anti-CD20 antibody and an alkylator, 94% of whom had exactly 2 prior therapies) across eight academic centers in the United States participating in the LEO Cohort Study (NCT02736357; https://leocohort.org/) showed a median PFS of approximately 1.4 years. Heterogeneity of third-line therapies observed in this real-world analysis reflects the absence of an outstanding standard of care for patients with R/R FL ≥2 prior therapies, with median PFS under 2 years for all third-line therapies, and response rate varying by type of third-line therapy (Casulo, 2021).

FL can also undergo histologic transformation to high-grade NHL that is clinically more aggressive at a rate of approximately 2-3% of patients with FL per year (rate of 19% over 8 years) (Link, 2013). Transformation is associated with poor survival outcome.

Management

Observation (watch-and-wait) is the standard practice for asymptomatic patients with low tumour burden FL. For advanced disease, the most frequently used first-line therapies include an anti-CD20 (rituximab or obinutuzumab) combined with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) or bendamustine.

No universally accepted standard of care for the treatment of R/R FL currently exists due to the highly diverse clinical course of the disease. Treatment of R/R FL is influenced by previous treatment regimens, duration of remission, performance status, and other factors. None of the available treatment options are considered curative.

Approved treatment options for R/R FL in the United States (US) include a combination of chemotherapy (e.g., bendamustine, doxorubicin) and an anti-CD20 monoclonal antibody (rituximab or obinutuzumab), immunomodulatory agent (lenalidomide) in combination with rituximab (R2), radioimmunotherapy (ibritumomab tiuxetane), phosphoinositide 3-kinase [PI3K] inhibitor (copanlisib), chimeric antigen receptor (CAR) T-cell therapies (axicabtagene ciloleucel [axi-cel], and tisagenlecleucel [tisa-cel]), and targeted therapies (mosunetuzumab and tazemetostat, an enhancer of zeste homolog 2 [EZH2] inhibitor).

Approved treatment options for R/R FL in the European Union (EU) include a combination of chemotherapy (e.g., bendamustine, doxorubicin) and an anti-CD20 monoclonal antibody (rituximab or obinutuzumab), immunomodulatory agent (lenalidomide) in combination with rituximab (R2), radioimmunotherapy (ibritumomab tiuxetane), PI3K inhibitors (idelalisib and duvelisib), chimeric antigen receptor (CAR) T-cell therapies (tisa-cel, axi-cel and liso-cel), inhibitor of Bruton's tyrosine kinase (BTK) (zanubrutinib) and bispecific antibody (mosunetuzumab).

Table 1: Overview of approved therapies for R/R FL

Therapy	Mechanism of Action	Indication	Major Efficacy Results			
			Response Evaluable Set (N)	ORR (%)	CR (%)	Median Duration of Response (months)
Full Approval						
Rituximab and Lenalidomide[a]	Chemoimmunotherapy	For the treatment of adult patients with previously treated FL (Grade 1-3A)	147	80	35	36.6
Bendamustine and Rituximab[b]	Chemoimmunotherapy	NA	114 (58 FL)	82	40	NL
Obinutuzumab + Bendamustine[c]	Chemoimmunotherapy	For the treatment for patients with FL who are refractory to or who did not respond or progress on a single-agent rituximab or rituximab-containing regimen.	155	79.7	15.7	NR
Ibritumomab tiuxetane[d]	Radio-immunotherapy	For the treatment of adult patients with rituximab relapsed or refractory CD20+ follicular B-cell NHL	73	80	30	13.9
Idelalisib[e]	PI3K inhibitor	For the treatment of adult patients with FL that are refractory to two prior lines of treatment	72	55.6	16.7	11.8
Duvelisib[f]	PI3K inhibitor	For the treatment of adult patients with FL that are refractory to at least two prior systemic therapies	73	40	0	10.0
Axicabtagene ciloleucel[g]	CAR T-cell therapy	For the treatment of adult patients with R/R FL after three or more lines of systemic therapy	75	91	77	38.6
Tisagenlecleucel[h]	CAR T-cell therapy	For the treatment of adult patients with R/R FL after two or more lines of systemic therapy	94	86.2	69.1	NR

Conditional marketing authorization						
Mosunetuzumab[i]	Bispecific antibody	For the treatment of adult patients with R/R FL who have received at least two prior systemic therapies	90	80.0	60.0	22.8

a. Leonard 2019. ORR and CR were IRC assessed using 2007 IWG (Cheson 2007). Note: 56% of subjects enrolled in the AUGMENT trial had only 1 line of prior anti lymphoma treatment. In addition, subjects enrolled in the AUGMENT trial were eligible to receive rituximab monotherapy.

b. Rummel 2016. Responses were based on 114 subjects in the iNHL cohort with 58 FL subjects (51%).

c. Gazyvaro SmPC was used as a source for efficacy analysis. ORR and CR were IRC assessed using 2007 IWG (Cheson 2007).

d. Zevalin SmPC was used as a source for efficacy analysis. ORR and CR were assessed by an independent panel of radiologists and oncologists (LEXCOR) according to IWRC (Cheson 1999).

e. Zydelig SmPC was used as a source for efficacy analysis. ORR and CR were IRC assessed using 2007 IWG (Cheson 2007).

f. Copiktra SmPC was used as a source for efficacy analysis. ORR and CR were IRC assessed using 2007 IWG (Cheson 2007).

g. Yescarta SmPC was used as a source for efficacy analysis where available. ORR and CR were IRC assessed per IWG Lugano classification (Cheson 2014).

h. Kymriah SmPC was used as a source for efficacy analysis where available. ORR and CR were IRC assessed per IWG Lugano classification (Cheson 2014)..

i. Lunsumio SmPC was used as a source for efficacy analysis where available. ORR and CR were IRC assessed using 2007 IWG for mosunetuzumab (Cheson 2007).

Despite existing therapies for R/R FL, there are challenges with the use of these therapies in specific settings, and more treatment options are needed for patients with R/R FL; therefore there is still an unmet medical need in this patient population.

2.1.2. About the product

Epcoritamab (GEN3013; DuoBody®-CD3xCD20) is a humanized immunoglobulin G1 (IgG1) bispecific antibody that binds to a specific extracellular epitope of CD20 on B-cells and to CD3 on T-cells.

The claimed new indication is: treatment of adult patients with relapsed or refractory follicular lymphoma after 2 or more lines of systemic therapy.

The MAH proposes a new, additional epcoritamab 3–step step-up dosing (SUD) regimen for the treatment of subjects with R/R FL. In this schedule, 3 mg is given as a second intermediate dose on D15, instead of the first full dose (48 mg) in the approved posology. This includes an initial priming dose of 0.16 mg on Cycle 1 Day 1 (C1D1), a first intermediate dose of 0.8 mg on Cycle 1 Day 8 (C1D8), a second intermediate dose of 3 mg on Cycle 1 Day 15 (C1D15), and a full dose of 48 mg on Cycle 1 Day 22 (C1D22).

Epcoritamab is administered by SC injection in treatment cycles of 28 days, with once weekly (QW) dosing in Cycles 1 to 3, once every 2 weeks (Q2W) dosing in Cycles 4 to 9, and once every 4 weeks (Q4W) dosing in Cycle 10 and thereafter, until unacceptable toxicity or disease progression.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

Clinical development program

Evaluation of the efficacy and safety of epcoritamab in R/R FL grades 1 to 3A (hereafter referred to as FL) is primarily based on results from pivotal Study GCT3013-01, an ongoing global, single-arm, Phase 1/2 study designed to evaluate epcoritamab as monotherapy in R/R B-NHL. Study GCT3013-01 is comprised of a Dose Escalation Part, an Expansion Part, and an Optimization Part. Key parts of the study that included subjects with FL are:

- Dose Escalation Part, including 1 subject with FL who was assigned to receive epcoritamab administered using a 2-step SUD regimen (0.16/0.8/48 mg). This subject was included in the primary safety analysis set.
- The iNHL expansion Part, includes 128 subjects with FL who were assigned to receive epcoritamab administered using a 2-step SUD regimen (0.16/0.8/48 mg). This cohort represents the pivotal efficacy analysis set (01 FL) and is included in the primary safety analysis set.
- FL Optimization Part, which evaluated 3-step SUD regimens including 86 subjects with FL who received epcoritamab using the proposed dosing regimen (0.16/0.8/3/48 mg), with the goal of reducing the incidence and severity of CRS among subjects with FL.

In addition, data from Study GCT3013-04, an ongoing Phase 1/2, open label, single-country, study of epcoritamab in Japanese subjects with R/R B-NHL, provides supportive efficacy and safety data for epcoritamab monotherapy in the intended indication.

Scientific advice

Scientific advice on the development of epcoritamab for the treatment of patients with relapsed or refractory FL was given from the CHMP on 25/06/2020 (EMEA/SA/4478/1/2020/III).

Regarding the need of a 3-month repeat dose toxicity study in cynomolgus monkeys and an embryofetal development toxicity study, the CHMP could agree that due to an anti-drug antibody response accompanied by loss of exposure in the very large majority of monkeys following repeat dosing, a 13 week toxicity study will be of limited value and could be waived. Regarding the embryofetal developmental study, the CHMP considered based on the weight of evidence, that epcoritamab has the potential to be transmitted from the mother to the developing fetus, and based on its MoA, fetal exposure to epcoritamab may cause adverse development outcomes including B-cell lymphocytopenia and alterations in normal immune responses in infants exposed in utero. Cynomolgus monkey is usually the current relevant nonhuman primate model for embryofetal developmental toxicity, it is unlikely that additional data derived from evaluation in a non-human primate embryo study would provide more useful information for hazard identification or pregnancy risk assessment in patients. Therefore, the proposal to waive the requirement for an embryofetal developmental toxicity study could be acceptable.

The CHMP acknowledged the remaining unmet medical need for R/R FL in spite that already other approved and/or recommended treatment options are available in the R/R FL setting. From a regulatory perspective, it was stated that for a conditional marketing authorization, the MAH needs to demonstrate that epcoritamab fulfils an unmet medical need. In case other products have already been authorized for the same indication, the MAH needs to provide appropriate data and arguments to support the claim that an unmet medical need still exists despite these treatments and that epcoritamab is able to fulfil that unmet medical need by bringing a major therapeutic advantage to patients in r/r FL over the existing treatment option(s) for which full marketing authorization has been granted.

Regarding the study design of Trial GCT3013-01, the CHMP recommended that inclusion criteria specifically define what is considered a relapsed or refractory disease. Further the MAH should consider to include also patients with ECOG PS of 2 besides those with ECOG 0-1, this would improve generalizability of study data.

The primary endpoint ORR assessed by IRC per Lugano criteria and secondary endpoints DOR, CR rate TTR, and PFS were considered acceptable. However, it was noted that in a single arm trial observed response is not necessarily an unbiased estimate of response rate in the full target population as the

open uncontrolled design involve several sources of bias, with patient selection having the largest impact.

The MAH is proposing to prospectively evaluate MRD at a central laboratory using an analytically validated methodology, which is acceptable, if the method is indeed validated. From the technical side, since the levels of ctDNA vary across different lymphoma subtypes, being higher in aggressive lymphomas than in indolent lymphomas (Rossi et al., 2019), the use of ctDNA for aNHL and PBMCs for iNHL cohort could be supported. The proposed clonoSEQ® assay for measuring MRD is based on a multiplex PCR and NGS methods and received the FDA approval for clinical use in ALL and MM. While the RQ-PCR and multiparametric flow cytometry (MPFC) are still considered the gold standard methods of MRD assessment in lymphoid malignancies (Monter et al., 2019), the clonoSEQ® assay may in principle be acceptable in the proposed settings. However, results might vary according to sample time within the course of the disease, by sampling site location, sample processing, and cell enrichment strategies (A. Monter et al., 2019). Although the results of several studies indicates that clonoSEQ® shows a strong correlation between MRD obtained by HTS and MPFC in ALL, MM and CLL, this has not yet been established in the proposed indications.

The justification and calculation of sample size was considered overall acceptable. However, it was noted that the proposed design does not correspond to standard two-stage design for Phase II trials, and the sample size is not fixed for at least one efficacy analysis by which it is unclear whether the Type I error would be controlled. Methods for obtaining appropriate estimates for treatment effect and confidence intervals with correct coverage would need to be pre-specified. Generally, and importantly, adaptive elements in a single arm trial setting and changes in the enrolled population could render study results uninterpretable due to the uncontrolled nature of the study and the complete plan would have to be finalized before start of the trial. Finally, the validity of the efficacy analysis for the overall iNHL population is questionable as this analysis would likely be driven by the treatment effect in the FL subgroup and the sample size would be too small to evaluate the consistency of treatment effect across other subtypes.

Finally given the single arm study design, the CHMP noted that no discussion on historical control for contextualization of study results was provided by the MAH. Although the challenges for undertaking a two arm trial were acknowledged, it was considered that even an underpowered RCT study would provide more robust demonstration of benefit than a single arm trial. The lack of a study with an active comparator should be justified, discussed at the time of the MAA.

The safety data will include approximately 480 patients (380 in monotherapy, 100 in combination (128 FL patients)) exposed to epcoritamab, which is rather limited. Nevertheless, considering the intended target population and the actual adverse effects, it may be acceptable.

Whether GCT3013-TBD of epcoritamab+R2 versus R2 alone, in patients with FL who are refractory to or have relapsed after prior therapy that included an anti-CD20 mAb-containing regimen, may serve as the confirmatory trial under a specific obligation for the proposed indication in R/R FL, will depend on remaining uncertainties after assessment of the MAA. The design of the phase 3 study was further discussed in the SA provided at 15 September 2022 (EMA/SA/0000095173).

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. 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.

2.2.2. Conclusion on the non-clinical aspects

Previous nonclinical data supports the intended clinical use of epcoritamab. In addition, epcoritamab is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The clinical trials were performed in accordance with GCP as claimed by the MAH.

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

Table 2: Tabular overview of clinical studies

Study number	Title	Countries where the trial is/was conducted	Study completion date
GCT3013-01	A Phase 1/2, Open-Label Safety Trial of GEN3013 in Patients with Relapsed, Progressive or Refractory B-Cell Lymphoma	Australia, Canada, Germany, Denmark, Spain, Finland, France, Italy, South Korea, Netherlands, Poland, Sweden, Singapore, United Kingdom, United States of America	Ongoing
GCT3013-04	Safety and Preliminary Efficacy of Epcoritamab in Japanese Subjects with Relapsed or Refractory B-NHL – A Phase 1/2, Open-Label, Dose-Escalation Trial with Expansion Cohorts	Japan	Ongoing

Study GCT3013-01 is an ongoing global, single-arm, Phase 1/2 study designed to evaluate

epcoritamab as monotherapy in R/R B-NHL. Study GCT3013-01 is comprised of a dose escalation part, an expansion part, and an optimization part.

In addition, data from Study GCT3013-04, an ongoing Phase 1/2, open label, single-country, study of epcoritamab in Japanese subjects with R/R B-NHL, provides supportive efficacy and safety data for epcoritamab monotherapy in the intended indication.

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 iNHL Expansion Part of Study GCT3013-01 and the FL Expansion Part of Study GCT3013-04 the epcoritamab 2-step up dosing (SUD) regimen (0.16/0.8/48 mg) was used. This dosing regimen includes an initial priming dose of 0.16 mg on cycle 1 Day 1 (C1D1), an intermediate dose of 0.8 mg on Cycle 1 Day 8 (C1D8) and a full dose of 48 mg (C1D15, C1D22, and thereafter).

The in the SmPC recommended dosing for the treatment of subjects with R/R FL, is the epcoritamab 3 SUD regimen that includes an initial priming dose of 0.16 mg on Cycle 1 Day 1 (C1D1), a first intermediate dose of 0.8 mg on Cycle 1 Day 8 (C1D8), a second intermediate dose of 3 mg on Cycle 1 Day 15 (C1D15), and a full dose of 48 mg on Cycle 1 Day 22 (C1D22). The 3 SUD regimen was used in the GCT3013-01, Optimization Part.

Epcoritamab is administered with once weekly (QW) dosing in Cycles 1 to 3, once every 2 weeks (Q2W) dosing in Cycles 4 to 9, and once every 4 weeks (Q4W) dosing in Cycle 10 and thereafter, until unacceptable toxicity or disease progression.

- 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

2.3.2. Pharmacokinetics

Results on epcoritamab pharmacokinetics (PK), pharmacodynamics (PD), and immunogenicity (ADA) in subjects with all B-NHL subtypes, LBCL subjects, and DLBCL subjects and were presented in the original marketing application. To support the current application in subjects with R/R FL, epcoritamab PK, PD, and ADA data were updated and summarized using data in subjects with FL from Studies GCT3013-01 and GCT3013-04.

An overview of the three parts of the pivotal study GCT3013-01 for FL with schedules of PK, pharmacodynamic, and safety assessments are presented in Table 3. The for DLBCL approved 2-step-up dosing regimen, consisting of a priming (0.16mg), intermediate (0.8 mg), and full dose (48 mg), was evaluated in the Dose Escalation and Expansion Parts of Studies GCT3013-01. The OPT Part of the GCT3013-01 trial was added to investigate different step-up dosing regimens along with adequate hydration and dexamethasone to further reduce the overall rate and severity of CRS. Two alternative 3-step-up dose regimens were selected for evaluation that included a second intermediate dose administered on C1D15 followed by a full dose on C1D22 and thereafter: Arm A of the FL OPT Part of the trial tested 3 mg as the second intermediate dose and Arm B tested 6 mg as the second intermediate dose.

Table 3: Overview of pharmacology program of study GCT3013-01 in subjects with FL

Title: A Phase 1/2, Open-Label, Dose-Escalation Trial of GEN3013 in Patients with Relapsed, Progressive or Refractory B-Cell Lymphoma		
Dose Escalation (Part 1, 68 Subjects Treated[a])	**FL Subjects in iNHL Expansion (Part 2, 128 Subjects Treated)**	**FL Subjects in Optimization (Part 3, 80 Planned)**
• Step up dosing. • Priming dose: 0.004, 0.0128, 0.04, 0.08, 0.16 mg • Intermediate dose: 0.25, 0.5, 0.76, 0.8 mg, 1.6 mg • Full dose: 0.0128, 0.04, 0.12, 0.38, 0.76, 1.5, 3, 6, 12, 24, 48, 60 mg Treatment cycles are 28 days. Dosing Schedule: Cycles 1 and 2: Days 1, 8, 15, and 22 (QW); Cycles 3 to 6: Days 1 and 15 (Q2W); Cycles 7 and beyond until unacceptable toxicity, progressive disease, or withdrawal of consent: Day 1 (Q4W)	• Step up dosing. • Priming dose: 0.16 mg • Intermediate dose: 0.8 mg • Full dose: 48 mg Treatment cycles are 28 days. Dosing Schedule: QW dosing in Cycles 1 to 3; Q2W dosing in Cycles 4 to 9; Q4W dosing in Cycle 10 and thereafter	• Step up dosing. • Priming dose: 0.16 mg • Intermediate dose: 0.8 mg • 2nd Intermediate dose: 3 mg (Arm A) or 6 mg (Arm B) • Full dose: 48 mg Treatment cycles are 28 days. Dosing Schedule: QW dosing in Cycles 1 to 3; Q2W dosing in Cycles 4 to 9; Q4W dosing in Cycle 10 and thereafter
PK: • 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	**PK:** • 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	**PK:** • At Predose, 6-14 hours (after dose), 1, 2, and 3 days after dose during 1st, 2nd dose and 3rd dose in Cycle 1 • At Predose, 1, 6 hours (after dose), 1 and 5 days after dose during 4th dose in Cycle 1 • At Predose, 1, 6-14 hours (after dose), 1 and 4 days after dose during 1st, 2nd, 3rd, and 4th dose in Cycle 2At Predose from in Cycle 2, 2nd dose and onward
• At Predose during 1st dose in Cycle 7 and onward	• At Predose and 1 hour (after dose) during 1st dose in Cycle 10 and onward	
ADA: • At screening • At Predose during 3rd and 4th dose in Cycle 1 • At Predose during 1st, 2nd, 3rd, and 4th dose in Cycle 2 • At Predose during 1st dose in Cycle 3 and onward	**ADA:** • At Predose during 1st and 4th dose in Cycle 1 • At Predose during 1st and 4th dose in Cycle 2 and 3 • At Predose during 1st and 3rd dose in Cycle 4-9 • At Predose during 1st dose in Cycle 10 and onward	**ADA:** • At screening • At Predose during 3rd and 4th dose in Cycle 1 • At Predose during 1st, and 4th dose in Cycle 2 • At Predose during 1st dose in Cycle 4, 8 and every 4th cycle starting Cycle 12
Cytokine: • At Predose, 6 hours (after dose), 1, 2, and 3 days during 1st, and 2nd dose in Cycle 1 • At Predose, 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	**Cytokine:** • At Predose during 1st, 2nd, and 4th dose in Cycle 1 • At Predose, 1 hour (after administration), and 1 day during 3rd dose in Cycle 1 • At Predose and 1 hour (after administration) during 1st and 2nd dose in Cycles 2-3	**Cytokine:** • At Predose, 6-14 hours (after dose), 1, 2, and 3 days after dose during 1st, 2nd dose and 3rd dose in Cycle 1 • At Predose, 1, 6-14 hours (after dose), 1 and 5 days after dose during 4th dose in Cycle 1 • At Predose, 1, 6-14 hours (after dose), 1 and 3 days after dose during 1st, dose in Cycle 2 • At Predose during the 2nd and 3rd dose of Cycle 2

Methods

The drug substance and drug product used for the treatment of subjects with R/R FL in Studies GCT3013-01 (including the FL optimization cohort) and GCT3013-04 were the same as those used for treatment of subjects with R/R LBCL as noted in the original application.

The analytical methods (epcoritamab quantification and ADA [anti-drug antibody] detection) used in Studies GCT3013-01, including the FL optimization cohort, and GCT3013-04 for the treatment of subjects with R/R FL were the same as those used for treatment of subjects with R/R LBCL in these studies as noted in the original application. Successful cross-validation results of analytical method ECLIA-139 performed at ICON Bioanalytical Laboratories, USA and ICON Bioanalytical Laboratories, NL were demonstrated. Interim bioanalytical reports were provided for studies GCT3013-01 and GCT3013-04 for ADA analysis, but not for GCT3013-01 optimisation part. A method qualification report for Nab testing was provided, but no Nab testing was carried out.

PopPK modelling (3L-FL-PopPK-2023 Report and GCT3013-01-OPT-FL Report)

PopPK report 3L-FL-PopPK-2023 describes the update of the previously developed and validated popPK model (3L-DLBCL-PopPK-2022) with PK data from subjects with FL from studies GCT3013-01 and GCT3013-04.

In total, 508 subjects from studies -01 (dose escalation and dose expansion parts) and -04 (dose escalation and dose expansion Arm 1 (monotherapy) received at least one dose of epcoritamab. Of those 508 subjects, 41 subjects did not have quantifiable (> lower limit of quantification [LLOQ]) post-dose PK observations, for 1 subject the concentration time profile was inconsistent with the dosing history. Thus, after excluding the subjects/samples above, data from 466 subjects contributing a total of 15683 quantifiable epcoritamab post dose concentration values were included in the model development. Of those 466 subjects, 424 subjects were administered the full dose of 48 mg.

As the prior model, the final covariate Model 210 was the QSS approximation of the two-compartment epcoritamab TMDD model with the first order SC absorption. In a reference subject (subject with the reference values of covariates and zero values of the individual random effects), epcoritamab PK parameters (Table 4) were similar to the previously estimated values. The covariates retained in the final model were WT on CL/F, Q/F, VC/F, and VP/F; age and BMI on k_a; tumour size (SUMPPD) and iNHL on k_{int}. Effects of weight and age were consistent with those estimated by the prior model (3L-DLBCL-PopPK-2022). In addition to the covariate effects identified in the prior analysis, the updated model included BMI effect on k_a, tumour size effect on k_{int}, and iNHL lymphoma subtype on k_{int}. Similarly, sex, Asian race, ADA, injection site, renal and hepatic function were tested during the model development and none of these had a statistically significant effect on epcoritamab PK after accounting for the body weight.

Table 4: Parameter estimates of Final Model 210 (3L-FL-PopPK-2023 report)

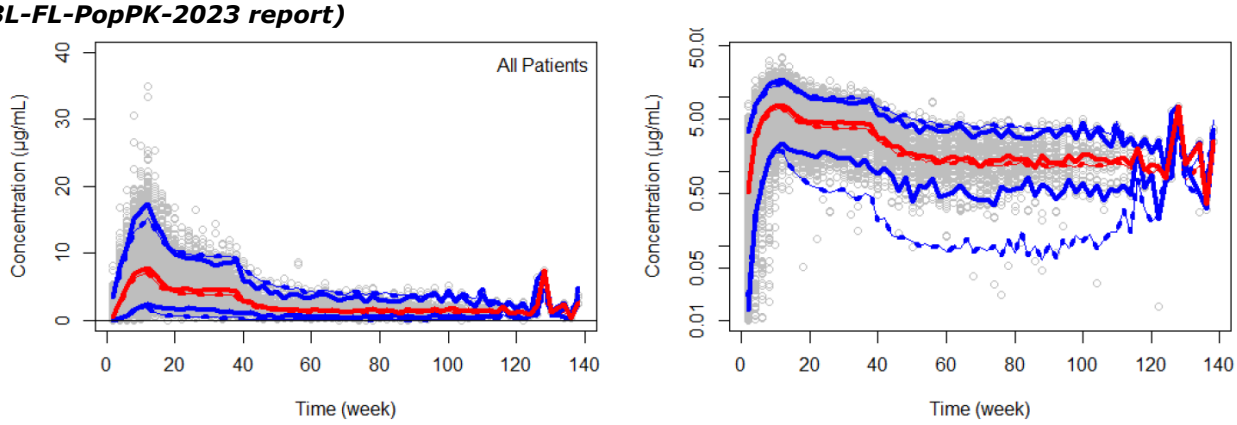
Parameter		Description	Value	RSE%	95% CI
CL/F (L/day)	θ_1	Apparent nonspecific clearance	0.526	2.15	0.504 ; 0.549
Q/F (L/day)	θ_2	Apparent inter-compartment clearance	0.527	4.91	0.476 ; 0.578
V_C/F (L)	θ_3	Apparent central volume	9.42	2.51	8.95 ; 9.88
V_P/F (L)	θ_4	Apparent peripheral volume	10.7	7.68	9.11 ; 12.3
k_a (1/day)	θ_5	Absorption rate constant	0.534	3.21	0.501 ; 0.568
BASE (µg/mL)	θ_6	Total target concentration	2.37	4.83	2.15 ; 2.6
K_{SS} (µg/mL)	θ_7	Quasi-steady-state constant	0.277	6.16	0.244 ; 0.31
k_{int} (1/day)	θ_8	Drug-target complex elimination rate	0.0253	9.13	0.0208 ; 0.0299
σ_{prop}	θ_9	Residual error: proportional part (CV)	0.164	1.36	0.16 ; 0.168
σ_{add} (µg/mL)	θ_{10}	Residual error: additive part (SD)	0.0151	2.84	0.0143 ; 0.016
CL_{WT}	θ_{11}	Weight effect on CL/F	0.949	8.81	0.786 ; 1.11
Q_{WT}	θ_{12}	Weight effect on Q/F	0.75	Fixed	-
$V_{C,WT}$	θ_{13}	Weight effect on V_C/F	0.641	14	0.466 ; 0.817
$V_{P,WT}$	θ_{14}	Weight effect on V_P/F	1	Fixed	-
$k_{a,age}$	θ_{15}	Age effect on k_a	-0.381	36.3	-0.651 ; -0.11
$k_{a,BMI}$	θ_{16}	BMI effect on k_a	-0.689	22.5	-0.993 ; -0.385
$k_{int,SUMPPD}$	θ_{17}	Tumor size (SUMPPD) effect on k_{int}	0.312	20.2	0.188 ; 0.435
$k_{int,iNHL}$	θ_{18}	Lymphoma iNHL subtype effect on k_{int}	0.484	13.4	0.357 ; 0.612

Parameter		Value	RSE%	95% CI	CV	Shrinkage
ω^2_{CL}	Ω_{11}	0.109	9.17	0.0892 ; 0.128	CV=33.0%	19.2%
ω^2_{Q}	Ω_{22}	0.541	10.3	0.432 ; 0.65	CV=73.6%	23.1%
ω^2_{VC}	Ω_{33}	0.139	8.47	0.116 ; 0.162	CV=37.3%	18.9%
ω^2_{VP}	Ω_{44}	1.2	11.4	0.932 ; 1.47	CV=109.5%	22.4%
ω^2_{ka}	Ω_{55}	0.231	9.77	0.187 ; 0.275	CV=48.1%	21.8%
ω^2_{BASE}	Ω_{66}	0.55	10.2	0.44 ; 0.659	CV=74.1%	21.6%
ω^2_{KSS}	Ω_{77}	1.03	10.2	0.824 ; 1.24	CV=101.5%	20.8%
ω^2_{kint}	Ω_{88}	0.999	11.1	0.782 ; 1.22	CV=100%	27.8%
$\omega^2_{\sigma 1}$	Ω_{99}	0.0552	7.27	0.0473 ; 0.063	CV=23.5%	3.2%
σ^2	Σ_{11}	1	fixed			2.0%

Abbreviations: 95% CI = 95% confidence interval; CV = coefficient of variation; iNHL = indolent B-cell non-Hodgkin lymphoma; NONMEM = Nonlinear Mixed-Effect Modeling software; RSE% = relative standard error = 100·abs(SE/PE); SD = standard; SE = standard error.
The NONMEM combined control and output file of Model 210 can be found in Appendix 9.2.1. The observed concentrations overlaid with the individual and population predictions for each subject can be found in Appendix 9.3.
Source: 210ParEst.csv (DiagnosticPlots.R)

The basic goodness of fit plots for Model 210 and VPC plots (Figure 1) showed a good agreement between the simulated and observed data, although the lowest 5th percentile was under-predicted by the model, as was also observed in previously submitted model in the original submission (3L-DLBCL-PopPK-2022).

Figure 1: Visual Predictive Check for observations following 48 mg doses, final model 210 (3L-FL-PopPK-2023 report)



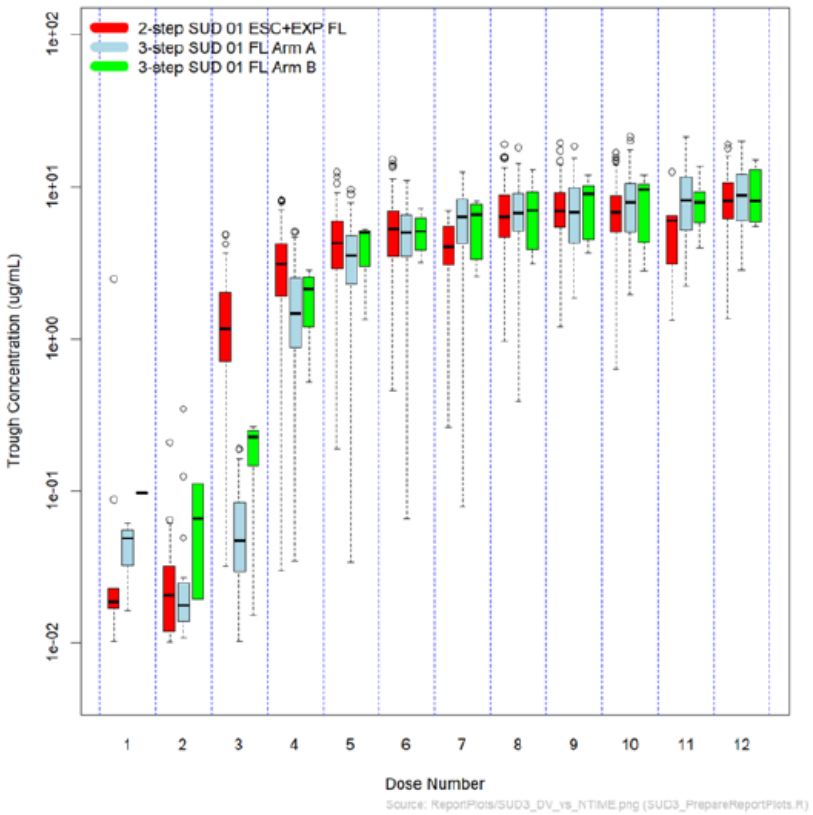
The solid lines are median (red), and 5th and 95th percentiles (blue) of observed epcoritamab concentrations on arithmetic scale (left) and semi-log scale (right). The solid-dashed lines show these quantities obtained by simulations. The simulated values were computed as medians of these statistics from 500 studies with dosing, sampling, and the covariate values of the analysis dataset. Time is time after the first dose.

PopPK report GCT3013-01-OPT-FL focussed on comparison of PK and PKPD of the approved 2-step with the alternative 3-step-up dose regimen. In total, 34 subjects from the FL OPT cohort received at least 1 dose of epcoritamab and had quantifiable postdose PK observations, including 28 subjects in Arm A and 6 subjects in Arm B. These subjects (a total of 931 quantifiable epcoritamab postdose concentration values) were evaluated as external validation with the analysis Model 210 of the main report (3L-FL-PopPK-2023 Report). The main goodness-of-fit and VPC plots confirmed an adequate fit of the data.

Results

Epcoritamab PK is similar between FL subjects who received the 3-step-up dosing regimen (N=75 in Arm A and N=6 Arm B) and FL subjects who received the 2-step-up dosing regimen (N=127) (Figure 2). As expected, data showed transiently lower trough concentrations after the second intermediate dose in FL subjects who received the 3-step-up dosing regimen compared to those after the first full 48 mg dose in FL subjects who received the 2-step-up dosing regimen. Comparable Ctrough values for the 3-step-up dosing regimen as for the 2-step-up dosing regimen were achieved from week 5 onwards.

Figure 2: Comparison of observed trough epcoritamab concentration in subjects with FL who received the 3-step-up dosing regimens vs the 2-step-up dosing regimen (GCT3013-01)



ESC = escalation; EXP = expansion; FL = follicular lymphoma; OPT = optimization; SUD = step-up dosing.

Values below the quantification limit were removed in the plots.

Red boxes: 2-step SUD ESC+EXP FL subjects (treated at 48 mg full dose), N=127.

Blue boxes: 3-step SUD FL Arm A, N=75.

Green boxes: 3-step SUD FL Arm B. Dose number 3 is different for 2-step SUD 01 ESC+EXP FL (48 mg) vs the other two which are the second intermediate dose (3 or 6 mg), N = 6.

Data cutoff date for GCT3013-01 ESC and EXP: 27 Feb 2023

Data cutoff date for GCT3013-01 OPT: 30 Nov 2023

As estimated by popPK analysis, pharmacokinetic exposures following QW, Q2W and Q4W epcoritamab dosing observed in subjects with R/R FL were similar to those reported in subjects with R/R LBCL/DLBCL (Table 5).

Table 5: Summary of predicted epcoritamab exposures for 48 mg dose QW administration (gMean (CV)) following 2 step-up dose regimen 0.16/0.8/48 mg or 3 step-up dose regimen 0.16/0.8/3/48 (compiled from Table 30 popPK report 3L-DLBCL-PopPK-2022 and Table 9 from GCT3013-01-OPT-FL report)

Exposure time/population dosing regimen	(D)LBCL (MAA) 2 step-up dose regimen (N=223)	FL 2 step-up dose regimen (N=127)	FL 3 step-up dose regimen (N=28)
Cycle 1 week 4			
Cmax (µg/mL)	4.5 (0.70)	3.4 (0.77)	1.5 (1.23)
AUCtau (µg/mL*day)	26.7 (0.73)	19.9 (0.84)	7.8 (1.25)
Ctrough (µg/mL)	3.3 (0.76)	2.7 (0.73)	1.3 (1.21)
QW dosing (Cycle 3 week 12)			
Cmax (µg/mL)	10.8 (0.41)	9.3 (0.41)	10.2 (0.51)
AUCtau (µg/mL*day)	69.3 (0.44)	59.7 (0.43)	65.4 (0.57)
Ctrough (µg/mL)	8.5 (0.51)	7.4 (0.47)	8.1 (0.70)
Q2W dosing			
Cmax (µg/mL)	7.5 (0.44)	6.3 (0.40)	6.6 (0.84)
AUCtau (µg/mL*day)	82.6 (0.51)	70.5 (0.44)	74.6 (0.98)
Ctrough (µg/mL)	4.1 (0.71)	3.6 (0.54)	3.9 (1.24)
Q4W dosing			
Cmax (µg/mL)	4.6 (0.62)	3.9 (0.56)	3.9 (1.09)
AUCtau (µg/mL*day)	72.5 (0.76)	62.5 (0.64)	66 (1.27)
Ctrough (µg/mL)	1.2 (1.26)	1.1 (100)	1.24 (1.77)

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.

Source: 154cond_exposureSummaryAll.csv (Compute_Nominal_48mg_Exposure.R)

154cond_Washout_Time_All.csv (Compute_Nominal_48mg_Washout.R)

Special populations

The impact of statistically significant covariates identified in the population PK analyses on epcoritamab model-predicted Cycle1-3 C_{avg} is presented below in Table 6. Consistent with the original model (3L-DLBCL-PopPK-2022), body weight was the main contributor to the inter individual variability of PK of epcoritamab. Dependence of absorption rate constant ka on BMI is not unusual for mAbs, with k_a decreasing with increasing BMI with the power coefficient of -0.689. Dependence of k_{int} on SUMPPD reflects increase of target-mediated elimination with increasing tumour size with the power coefficient of 0.312. Approximately two times lower k_{int} in patients with iNHL reflects decrease of target-mediated elimination in patients with less aggressive disease. The covariate effects on k_{int} do not have meaningful effect on the steady-state exposure since starting from Cycle 2 approximately 90% of the drug was eliminated through the linear nonspecific pathway.

Table 6: Summary of effect of covariates on epcoritamab C_{avg} (Cycle 1-3) (final Model 210)

Covariate and parameter	Level	N	Mean (SD)	Geometric Mean (CV)	Median (Range)	Percent Difference of Geometric Mean Values[a]	
						Exposure	Weight[b]
Age group (Significant on k_a)	< 65 years	197	5.78 (2.59)	5.16 (0.539)	5.42 (0.659-12.4)	-10.2	6.1
	≥ 65, < 75 years (Reference)	175	6.37 (2.61)	5.75 (0.546)	6 (0.368-16.6)	0	0
	≥ 75 years	94	6.53 (2.85)	5.89 (0.523)	6.21 (0.955-20.2)	2.4	-2.9
Weight group (Significant on CL, Q, V_C, V_P)	< 65 kg	152	7.75 (2.89)	7.15 (0.459)	7.46 (1.16-20.2)	31.9	-24.4
	65-85 kg (Reference)	190	5.91 (2.2)	5.42 (0.494)	5.67 (0.368-12.4)	0	0
	≥ 85 kg	124	4.56 (1.83)	4.14 (0.515)	4.59 (0.447-11.3)	-23.6	32
BMI group, by median (Significant on k_a)	< 24.9 kg/m^2 (Reference)	233	7.16 (2.84)	6.55 (0.469)	6.91 (1.16-20.2)	0	0
	≥ 24.9 kg/m^2	233	5.15 (2.04)	4.65 (0.541)	5.11 (0.368-11.3)	-29	39.3
Tumour size, by median (Significant on k_{int})	< 31.8 cm^2 (Reference)	233	6.69 (2.71)	6.08 (0.497)	6.26 (0.955-16.6)	0	0
	≥ 31.8 cm^2	233	5.62 (2.52)	5.01 (0.564)	5.49 (0.368-20.2)	-17.5	4.4
Lymphoma subtypes (Significant on k_{int})	LBCL (Reference)	223	6.79 (2.68)	6.25 (0.45)	6.42 (0.659-20.2)	0	0
	R/R FL	158	5.91 (2.39)	5.43 (0.453)	5.45 (0.992-13.6)	-13.2	9.8
ADA status (Not significant)	Negative (Reference)	444	6.14 (2.66)	5.52 (0.527)	5.74 (0.447-20.2)	0	0
	Positive	22	6.5 (2.85)	5.57 (0.816)	5.87 (0.368-11.6)	0.9	2.7

ADA = anti-drug antibody; BMI = body mass index; C_{avg} = average concentration time; CV = coefficient of variation; LBCL = large B-cell lymphoma; N = number of subjects; SD = standard deviation; R/R FL = relapsed or refractory follicular lymphoma 1 to 3A (FL 3B not included); k_a = absorption rate constant; CL = clearance of epcoritamab (L/day); Q = inter-compartmental clearance; V_c = volume of epcoritamab central compartment (L); V_p = volume of epcoritamab peripheral compartment (L); k_{int} = elimination rate constant of the drug-target complex a. Compared to reference category (reference category is the one with zero differences in each covariate group). b. Body weight compared to body weight of the reference category.

2.3.3. Pharmacodynamics

Mechanism of action

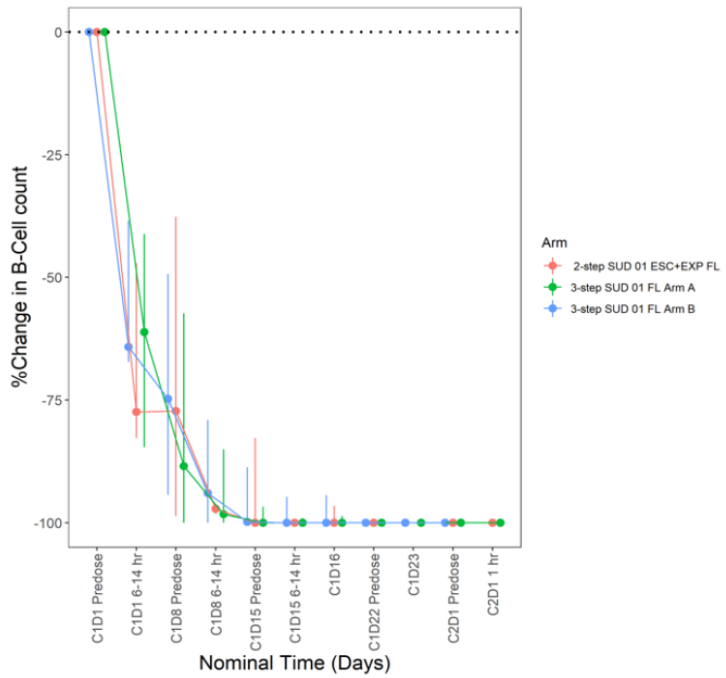
Epcoritamab is a bispecific antibody, recognizing the T-cell antigen CD3 and the B-cell antigen CD20. Epcoritamab's mechanism of action is induction of T-cell-mediated cytotoxicity of CD20-expressing cells, and associated T-cell activation and proliferation, upon simultaneous binding to CD20 on target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

Primary and Secondary pharmacology supporting alternative dosing

The OPT Part of the GCT3013-01 trial was added to investigate different step-up dosing regimens to further reduce the overall rate and severity of CRS. Two alternative 3-step-up dosing regimens were selected for evaluation that included a second intermediate dose administered on C1D15 followed by a full dose on C1D22 and thereafter: Arm A of the FL OPT Part of the trial tested 3 mg as the second intermediate dose and Arm B tested 6 mg as the second intermediate dose. The OPT part of study GCT3013-01 is ongoing, inclusion of 80 subjects is planned. Preliminary data for B-cell depletion and IL-6 release from 36 subjects are available. An updated report with the final dataset was submitted in response to the questions. A total of 86 subjects were treated in Arm A and 6 subjects in Arm B. Of these, all 86 subjects in Arm A and 6 subjects in Arm B were safety evaluable, and 75 subjects in Arm A and 6 subjects in Arm B were PK evaluable. Data for B-cell depletion was available for all 86 subjects in Arm A and 6 subjects in Arm B, and IL-6 data were available in all 92 subjects (Arm A and Arm B).

As shown in Figure 3, a rapid, deep, and sustained depletion of circulating peripheral B cells (CD19+) was observed in FL subjects who received the 3-step-up dosing regimen (N=86 in Arm A and N=6 Arm B) comparable to FL subjects who received the 2-step-up dosing regimen (N=127).

Figure 3: Comparison of B-Cell median percent change from baseline in subjects with FL who received the 3-Step (N=86, Arm A and N=6, Arm B) vs the 2-Step-up (N=127) dosing regimens (GCT3013-01)



C = cycle; D = day; ESC = Escalation; EXP = Expansion; FL = follicular lymphoma; OPT = optimization; SUD = step-up dosing.

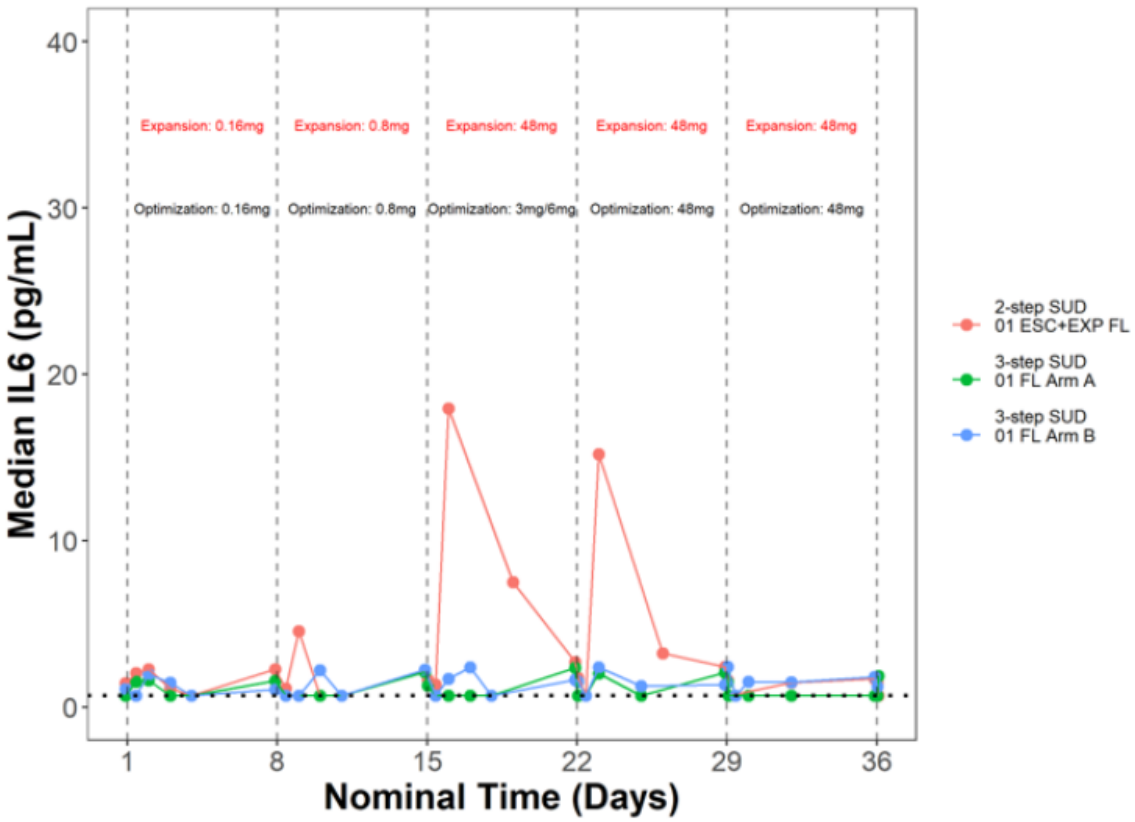
Lines show medians of B-cell percent change from baseline. Vertical bars show interquartile ranges.

Data cutoff date for GCT3013-01 ESC and EXP: 27 Feb 2023

Data cutoff date for GCT3013-01 OPT: 8 Jan 2024

The median IL-6 profile over nominal time and absolute IL-6 levels following the first full dose was compared between FL subjects who received the 3-step or 2-step-up dosing regimen. Median IL-6 were consistently low after the priming (C1D1), first intermediate (C1D8), second intermediate (C1D15), and first full dose (C1D22), and beyond, whereas median IL-6 levels appeared to increase after the first full dose on C1D15 in FL subjects who received the 2-step-up dosing regimen (N=128) (Figure 4).

Figure 4: Median IL-6 concentrations in subjects with FL who received the 3-step (N= 86, Arm A=3 mg, N=6, Arm b= 6 mg) vs the 2-step-up (N=127) dosing regimen (GCT3013-01)



ESC = escalation; EXP = expansion; IL-6 interleukin-6; FL = follicular lymphoma; OPT = optimization
SUD = step-up dosing.

Data cutoff date for GCT3013-01 ESC and EXP: 21 Apr 2023

Data cutoff date for GCT3013-01 OPT: 8 Jan 2024

2.3.4. PK/PD modelling

Alternative dosing: 3 step-up dosing regimen

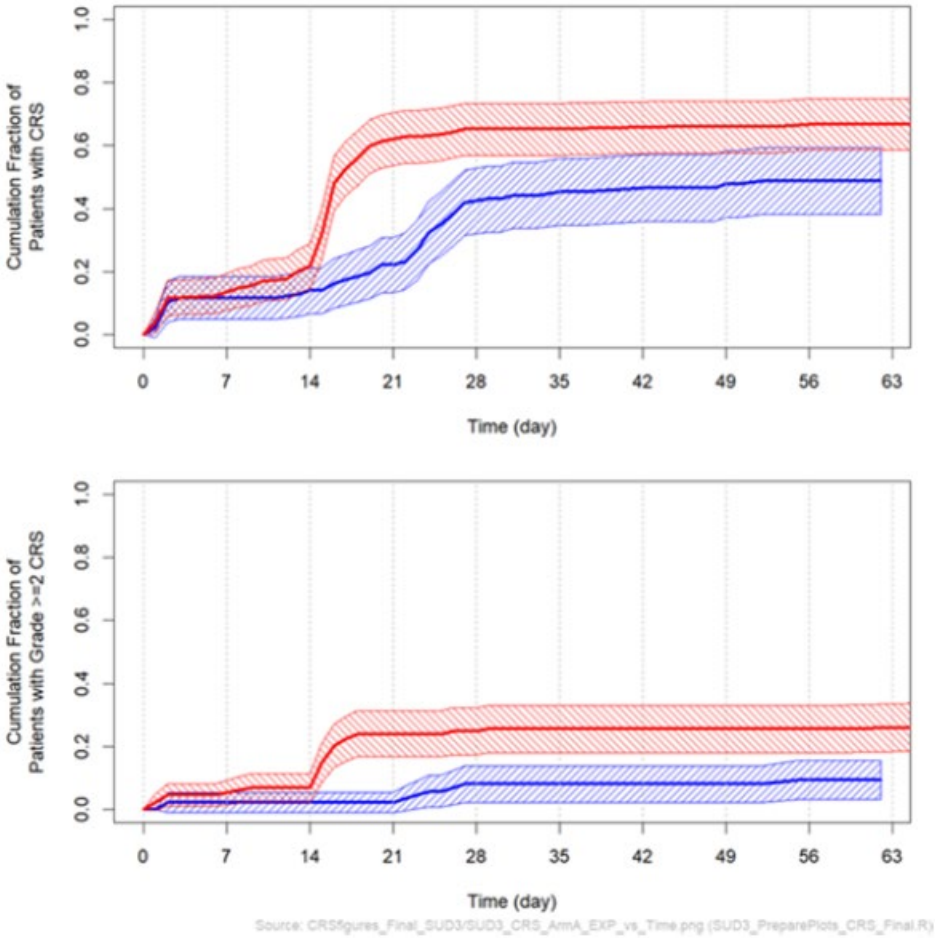
Relationships between epcoritamab exposures and CRS and IL-6 release were explored comparing the 3 step-up dosing regimen in OPT part from study GCT3013-01 with the 2 step-up dosing regimen from study GCT3013-01 (ESC and EXP parts) in FL population.

The relationship between epcoritamab exposures and any grade CRS, grade ≥2 CRS, CRS requiring tocilizumab was evaluated in exposure-safety analyses in FL subjects who received the 3 step-up dosing regimen. The proportion of subjects having at least 1 TEAE by quartiles of Cycle 1 AUC are presented in Table 7. There was no apparent exposure-response relationship between exposure and CRS risk in FL subjects who received the 3 step-up dosing regimen. The incidence of CRSwas lower with the 3-step-up dosing regimen 48.9% compared to 66.7% with the 2-step-up dosing regimen. For more details see safety part of this report.

Table 7: Summary of cytokine release syndrome by quartiles of exposure (Cycles 1 AUC) in subjects with FL who received the 3 step-up dosing regimens (GCT3013-01 OPT)

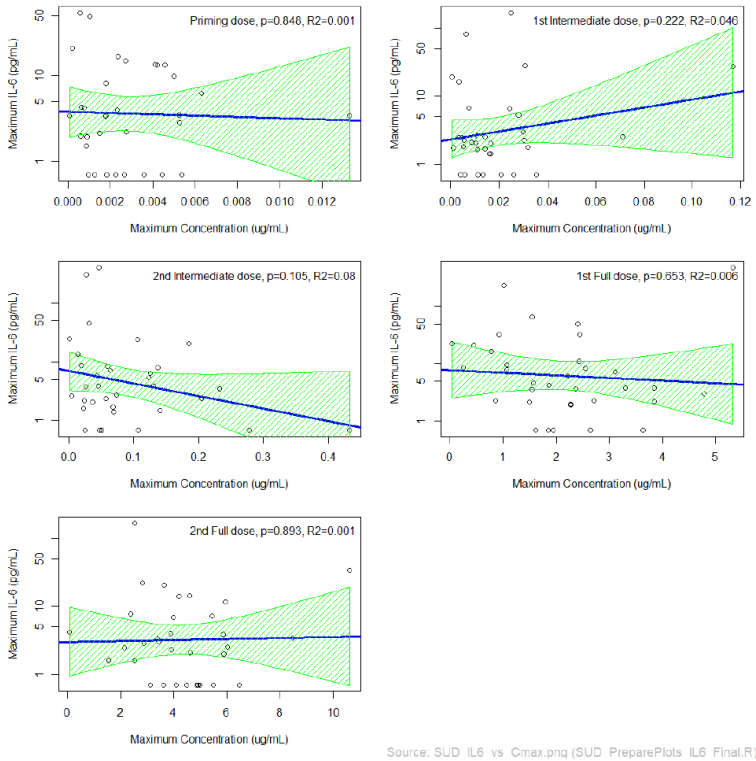
Consistent with the clinical analysis for CRS and results from N=30 analyses, the cumulative risk analysis indicates that the addition of a second intermediate dose in Arm A of the 3 step-up dosing regimen (0.16/0.8/3/48 mg) (N=86), along with adequate hydration and prophylactic dexamethasone, reduced the frequency and severity of CRS, as illustrated in Figure 5 compared to subjects with FL who received the 2 step-up dosing regimen (0.16/0.8/48 mg) (N=129).

Figure 5: Cumulative fraction of subjects with CRS events vs time (subjects with FL who received the 3 step-up dosing regimen in Arm A [N=86] vs subjects with FL who received the 2 step-up dosing regimen [N=129])



Regression models of IL-6 versus Cmax following each dose type (priming dose, first intermediate dose, second intermediate dose, first full dose, second full dose) were investigated. No significant correlation between observed peak IL-6 levels and predicted Cmax is seen during the 5 dosing periods up to the second full dose in FL subjects who received the 3-step-up dosing regimen.

Figure 6: Regression model of observed maximum IL-6 vs predicted Cmax in subjects with FL who received the 3-step step-up dose regimen (GCT3013-01 OPT)



Source: SUD_IL6_vs_Cmax.png (SUD_PreparePlots_IL6_Final.R)

Abbreviations: C_{max} = maximum concentration; ESC = escalation; EXP = expansion; IL-6 interleukin-6; FL = follicular lymphoma; OPT = optimization; PK = pharmacokinetic(s); SUD = step-up dosing.
Data cutoff date for GCT3013-01 ESC and EXP: 27 Feb 2023 for PK and 21 Apr 2023 for clinical data
Data cutoff date for GCT3013-01 OPT: 07 Jul 2023 for PK and 31 Jul 2023 for clinical data

In addition, similar exposure-response analyses were performed to assess the relationships between epcoritamab exposure and efficacy and safety in subjects with FL as were conducted for (D)LBCL at MAA.

Across the full dose range studied (0.12 to 48 mg), statistically significant ($p<0.05$) relationships between key efficacy endpoints (ORR, CR rate, PFS, and OS) and epcoritamab exposure were observed, i.e., higher epcoritamab exposures provided higher ORR/CR rate and longer PFS/OS in subjects with R/R FL.

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), probability of neutropenia and injection site reactions increased with increasing epcoritamab exposure ($p<0.05$), however, 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. The probabilities of the other AEs did not increase with increasing epcoritamab exposure.

Immunogenicity

In Study GCT3013-01 (ESC + EXP), on-treatment ADA status was positive for 3 of 120 (2.5%) subjects with FL who received the 48 mg full dose (see Table 8). All 3 subjects were ADA positive at 1 time point whilst ADA negative all other time points. Of 71 immunogenicity-evaluable subjects in Arm

A of the FL optimization cohort of study GCT3013-01, on-treatment ADA status was positive for 5 (7.0%) subjects. None of the positive evaluations had titer ≥1. In study GCT3013-04, 1 out of 21 subjects scored positive ADA. Nabs have not been tested.

Table 8 Summary of anti-drug antibody assessment (48 mg dose)

In the PopPK analysis, no meaningful differences in PK were detected between ADA negative and ADA-positive subjects after adjusting for other covariates.

2.3.5. Discussion on clinical pharmacology

To support the current application in subjects with R/R FL, epcoritamab PK, PD, and ADA data were updated with data from the Escalation (ESC), Expansion (EXP), and Optimization (OPT) Parts of Studies GCT3013-01 and GCT3013-04. The assessment of clinical pharmacology focused on the characterization of PK and PD of epcoritamab, evaluation of factors affecting PK using a population-modelling approach, immunogenicity, and exposure-response relationships of epcoritamab to support the selected dosing regimen.

PK results for subjects with FL were comparable to those in subjects with R/R (D)LBCL. Consistent with previous analyses of epcoritamab and results with other therapeutic antibodies, body weight had a statistically significant effect on the exposure of epcoritamab in subjects with FL. Subjects who weighed < 65 kg at baseline had the highest Cycle 1-3 Cavg, which was 31.9% higher than in subjects who weighed from 65 to < 85 kg. Subjects who weighed ≥ 85 kg had the lowest Cycle 1-3 Cavg, which was 23.6% lower than in subjects who weighed 65 to < 85 kg. Additional analyses of subjects with the 90% highest body weight i.e. 13 subjects with body weight > 105 kg, showed that the exposure was less than 20% lower in these subjects for the first 3 cycli. No difference in observed response rate was apparent. Hence, the proposed posology is also adequate for subjects with high body-weight.

Exposure-response analysis for efficacy and safety in subjects with FL were comparable to those in subjects with (D)LBCL. Hence, these exposure-response analyses support the 48 mg as a dose with acceptable efficacy and safety.

Immunogenicity was relatively low, with positive on-treatment ADA status for 3 of 120 (2.5%) subjects with FL who received the 48 mg full dose in the escalation and expansion parts of study GCT3013-01. In Arm A of the FL optimization cohort of study GCT3013-01, on-treatment ADA status was positive for 5 of 71 (7.0%) subjects. Only transient ADA positivity was observed. Preliminary immunogenicity results from the FL optimization cohort of GCT3013-01 were provided in the course of the procedure , however, no further description of the samples obtained from the optimization part but only samples from the escalation and expansion part are described. Thus, the interim report is seen as somewhat lacking in terms of the description of the analysis of the FL optimization cohort samples. While a method qualification report for a Nab assay has been submitted, no Nab measurement has been performed. The absence of Nab results makes the interpretation of the significance of the observed ADA levels challenging. However, the incidence of ADAs in both the expansion and optimizing cohorts of study GCT3013-01 is relatively modest and therefore not considered a major concern.

The OPT Part of the GCT3013-01 trial was added to investigate a 3-step-up dosing regimen including a second intermediate dose administered on C1D15 followed by a full dose on C1D22 (0.16/0.8/3/48mg) along with adequate hydration and dexamethasone to further reduce the overall rate and severity of CRS. The 3-step-up dosing regimen seems to lead to a reduction in mean cumulative CRS risk over time compared with the 2-step SUD regimen. Also median IL-6 levels remained consistently low whereas median IL-6 levels increased after the first full dose on C1D15 in subjects who received the 2-

step-up dosing regimen. Using this 3-step-up procedure exposure of epcoritamab is lower following the 3rd and 4th epcoritamab administration and is comparable to the 2-step-up dosing regimen thereafter. Therefore, the 3-step-up dosing regimen is not expected to impact efficacy.

2.3.6. Conclusions on clinical pharmacology

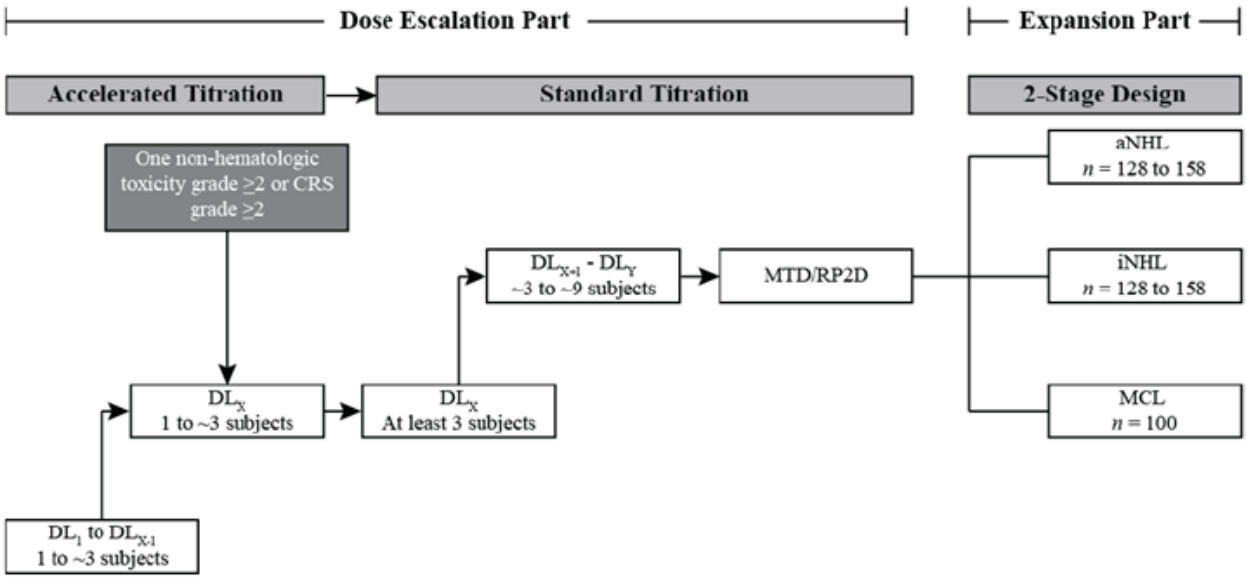
The clinical pharmacology data provided are sufficient to support the indication, relevant information has been included in the PI.

2.4. Clinical efficacy

Evaluation of efficacy in this application is based on clinical data from pivotal Study GCT3013-01 and supportive Study GCT3013-04. Both studies enrolled subjects with R/R FL who received at least 2 prior systemic therapies, which is the target population for this application.

GCT3013-01 is an open-label, phase 1/2 trial in patients aged 18 years or older with relapsed, progressive and/or refractory (R/R) mature B-cell lymphoma. The trial include 3 parts a Dose Escalation Part, an Expansion Part and an Optimization Part. The expansion part of the trial include 3 cohorts: aNHL, iNHL and MCL. The trial design for the Dose Escalation Part and Expansion Part is illustrated in Figure 7.

Figure 5: Overview of Dose Escalation and Expansion 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; Y = the highest investigated dose level.

The iNHL Expansion Part of Study GCT3013-01 and the FL Expansion Part of Study GCT3013-04 evaluated the epcoritamab 2-step SUD regimen (0.16/0.8/48 mg) in subjects with FL.

The FL Optimization Part of Study GCT3013-01 evaluated the proposed 3 step SUD regimen (0.16/0.8/3/48 mg) in subjects with FL. Together, these studies provide data to characterize epcoritamab efficacy in the target population of patients with R/R FL.

2.4.1. Dose response study(ies)

GCT3013-01 Trial – dose escalation part

The recommended phase 2 dose (RP2D) is based on the dose escalation part of study GCT3013-01 that is already assessed during the original application of epcoritamab for treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy (EMEA/H/C/005985/0000; EPAR EMA/CHMP/419797/2023 d.d.20 July 2023).

The recommended dose in the SmPC is based on results of the Optimization Part of Study GCT3013-01, that is discussed later on in this report (supportive studies).

2.4.2. Main study(ies)

A Phase 1/2, Open-Label, Dose-Escalation Trial of GEN3013 in Patients With Relapsed, Progressive or Refractory B-Cell Lymphoma-INHL cohort

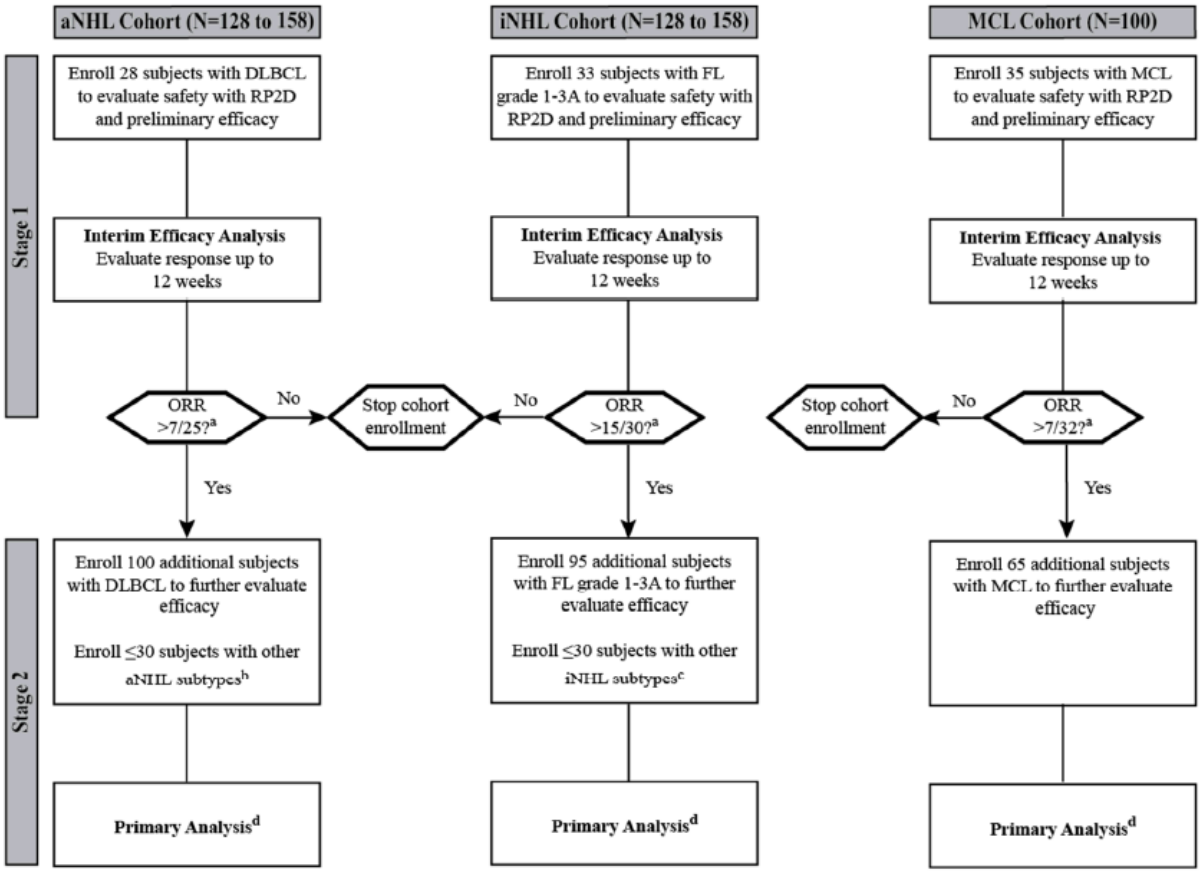
Methods

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, an Expansion Part and an Optimization Part. The expansion part is considered to be the pivotal study by the MAH.

The aim of the Expansion Part of this trial was to evaluate the efficacy and safety of epcoritamab using the RP2D regimen. The Expansion Part of the trial was initiated with parallel enrollment in 3 cohorts of subjects with distinct B-cell lymphoma subtypes: R/R aNHL cohort (LBCL), R/R iNHL cohort (including FL Grade 1-3A), and R/R MCL cohort who were treated with the RP2D of epcoritamab.

The iNHL Expansion Part was conducted in 2 stages (Figure 8). In Stage 1, only subjects with R/R FL Grade 1-3A were enrolled in the iNHL cohort, and response data was collected. Following an interim futility analysis, additional subjects with iNHL could be enrolled for Stage 2, including subjects with other iNHL subtypes (i.e., SLL, MZL). The primary analysis was planned to be conducted approximately 9 months after the last patient's first dose. For the iNHL cohort, the primary subtype (FL Grade 1-3A) was planned to be analyzed first, and then the overall iNHL population was to be analyzed.

Figure 6: GCT3013-01 Expansion Scheme



a. For the interim analysis, response was determined by Lugano criteria and assessed by the investigator and sponsor based on available data (e.g., efficacy, safety, pharmacodynamics, biomarkers). The denominator for the interim analysis accounted for a 10% dropout rate.

b. Other aNHL subtypes include high grade B-cell lymphoma, primary mediastinal B-cell lymphoma, and FL Grade 3B.

c. Other iNHL subtypes include marginal zone lymphoma and small lymphocytic lymphoma.

d. For primary analysis, response was determined by Lugano criteria and assessed by IRC.

Study participants

The **main inclusion criteria** were:

- Patient must be 18 years of age or older. Note; In countries were the legal age is 21 years of age; only patients 21 years of age or older are eligible
- 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
    - Expansion and optimization parts; histologic confirmed FL grade 1, 2 or 3A at initial diagnosis without clinical or pathological evidence of transformation
    - For the expansion part only; patients with marginal zone lymphomas (nodal, extranodal and splenic) might be included

    - For the expansion part only; patients with small lymphocytic lymphoma might be included

- 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.
- Previously treated with an alkylating agent or lenalidomide.
- Relapsed or refractory to the last prior line therapy. Previous lymphoma therapy is defined as 1 of the following/Lg; at least 2 months of single-agent therapy, at least 2 consecutive cycles of combination therapy, autologous HSCT, immunomodulatory therapy or radio immunotherapy.
- Patients must have had measurable disease
    - Fluorodeoxyglucose (FDG)-avid lymphomas; computerized tomography (CT) (or magnetic resonance imaging (MRI) scan with involvement of 1 or more clearly demarcated lesions/nodes with a long axis >1.5 cm and short axis >1.0 cm (or 1 clearly demarcated lesion/nod with a long axis>2.9 cm and short axis ≥1 cm) and FDG positron emission tomography (PET) scan that demonstrates positive lesion(s) compatible with CT (or MRI) defined anatomical tumour sites.
    - FDG-non avid lymphomas; CT (or MRI) scan with involvement of 2 or more clearly demarcated lesions/nodes with a long axis >1.5 cm and short axis >1cm or clearly demarcated lesions/node with a long axis >2.0 cm and short axis ≥ 1cm.
- ECOG performance status 0, 1 or 2.
- Adequate blood values; lymphocyte count <5x 10^9/L platelet counts ≥75x10^9/L, absolute neutrophil counts ≥1.0x10^9/L
- Patients must meet the following criteria regarding time since previous anti-neoplastic agent(s):
    - At least 4 weeks from last dose of non-investigational systemic chemotherapy (except when used as bridging therapy during screening in MCL cohort)
    - At least 4 weeks of 5 half-lives from last dose of other non-investigational antineoplastic agents, whichever is shorter (except anti-CD20 mAb or Bi-specific T-cell engagers (BiTE))
    - At least 5 half-live from last dose of investigational agents except for prior chimeric antigen receptor T-cell (CAR-T) therapy from which 30 days must pass prior to first epcoritamab administration.
- Resolution of toxicities from prior therapy to a grade that does not contraindicate trial participation in the opinion of the investigator.

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, Creatinine clearance <45 mL/min.
- Known clinically significant cardiac disease, including:
    - Onset of unstable angina pectoris within 6 months of signing ICF
    - Acute myocardial infarction within 6 months of signing ICF
    - Congestive heart failure (grade III or IV as classified by the New York Heart Association and/or known decrease ejection fraction of <45%.
- Chronic ongoing infectious diseases (except hepatitis B or hepatitis C) requiring treatment (excluding prophylactic treatment) at the time of enrolment or within the previous 2 weeks prior to the first dose of epcoritamab.
- Confirmed history or current autoimmune disease or other diseases resulting in permanent immunosuppression or requiring permanent immunosuppressive therapy. Low-dose prednisolone for rheumatoid arthritis or similar conditions is allowed.
- Seizure disorder requiring therapy (such as steroids or anti-epileptics).
- Any prior therapy with an investigational bispecific antibody targeting CD3 and CD20.
- Prior treatment with chimeric antigen receptor T-cell (CAR-T) therapy within 30 days prior to first epcoritamab administration.
- Eligible for curative intensive salvage therapy followed by high dose chemotherapy with HSCT rescue.
- Autologous HSCT within 100 days prior to first epcoritamab administration, or any prior allogeneic HSCT or solid organ transplantation.
- Active hepatitis B or ongoing hepatitis C infection .
- Known HIV infection.
- Exposed to live or live attenuated vaccine within 4 weeks prior to signing informed consent form (ICF)

Treatments

Epcoritamab was administered by SC injection in treatment cycles of 4 weeks, i.e., 28 days.

During the Expansion Part of the trial, 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)

Subjects were hospitalized for at least 24 hours after the first full dose of epcoritamab in cycle 1. This planned hospitalization was not reported as an SAE.

A re-priming cycle was required if the epcoritamab dose was delayed at certain timepoints beyond a specified number of days or weeks, depending on the time point on treatment. A re-priming cycle consisted of a weekly schedule of a priming dose, intermediate dose, and 2 full doses.

Premedication Prior to Epcoritamab Administration - Expansion Part

Subjects were premedicated with corticosteroids (i.e. prednisolone 100 mg IV), antihistamines (diphenhydramine 50 mg IV or oral or equivalent), and antipyretics (paracetamol (acetaminophen)

650 to 1000 mg PO or equivalent) 30 to 120 minutes prior to the first 4 doses of epcoritamab (i.e., priming, intermediate, and first 2 full doses). For subsequent doses of epcoritamab, premedication and cytokine release syndrome (CRS) prophylaxis were optional.

Prednisolone 100 mg IV were administered following epcoritamab administration on Day 2, Day 3, and Day 4 in conjunction with all 4 doses of epcoritamab in C1 (i.e., priming, intermediate, and first 2 full doses).

Corticosteroid that exceeded a total daily dose of 10 mg of prednisolone or equivalent administered for more than 10 days were prohibited during the trial, unless for the management of AEs (excluding corticosteroids given as prophylactic corticosteroid administration pre- and post-epcoritamab administration or concomitant medication for CRS).

If CRS ≥ Grade 2 occurred following the fourth epcoritamab administration on C1D22, corticosteroid administration on the day of and for 3 days following epcoritamab administration was continued for subsequent epcoritamab doses until a dose was given after which no CRS occurred. Otherwise, 4-day consecutive corticosteroids were administered following epcoritamab dosing only for C1 and for any re priming cycles.

Concomitant Therapy

Concomitant medications were allowed to provide adequate subject care and were given as clinically indicated, except for anti-lymphoma therapy. All concomitant medications were recorded except for vitamins or nutrient supplements. Supportive medications such as premedication, anti-viral medication, and anti IL6R were provided by the trial site.

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 (e.g., intravenous administration of tocilizumab).

Subjects considered to have an increased risk for clinical tumour lysis syndrome (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.

Prophylactic antibiotic, antiviral and antifungal therapies were allowed, unless medically contraindicated. The use of growth factors for neutropenia such as granulocyte colony stimulating factor was allowed during treatment with epcoritamab.

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 further evaluate clinical efficacy

• 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

Exploratory objectives were:

• To evaluate biomarkers predictive of clinical response to epcoritamab

• To evaluate pharmacodynamic markers linked to the mechanism of action of epcoritamab

• 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 (i.e. AEs, laboratory parameters (biochemistry, hematology including immunophenotyping for absolute T-cell and B-cell counts as well as T-cell activation and exhaustion markers, hospitalizations and cytokine measures),

• PK parameters (clearance, volume of distributed C_{max}, T_{max}, through concentration and half-life), incidence of ADAs to epcoritamab, changes in lymphoma symptoms as measured by the FACT-Lym

• changes in lymphoma symptoms as measured by the FACT-Lym

Exploratory endpoints are:

• Expression of CD3, CD20, and other molecular and genetic markers in tumour biopsies pretreatment and during treatment, and immune subpopulations in tumours and blood

• Plasmacodynamic markers in blood samples and within tumour (on-treatment biopsy)

• Duration of complete response (DOCR) by Lugano criteria as assessed by IRC

• Changes in well-being and general health status as evaluated by FACT-Lym and EZ-5D-3L, respectively and through qualitative interview

Efficacy evaluations were conducted as specified in the visit assessment schedule of the protocol, 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. All efficacy assessments were conducted throughout the trial until disease progression or withdrawal of consent from trial participation.

Health-related quality of life was assessed through the FACT-Lym and EQ-5D-3L PRO instruments on Day 1 of C1, C3, C5, C7, and C9 and at the end of treatment visit. In addition, 6 questions from the FACT-Lym (P2 [body pain], BRM3 [fever], ES3 [night sweats], GP1 [lack of energy], BMT6 [tires easily], and C2 [weight loss]) related to key symptoms of lymphoma were assessed on Day 1 of C2, C4, C6, C8, and C10, and every cycle thereafter until the end of treatment.

Primary estimands

Study intervention: SC injection of Epcoritamab 48 mg as full dose in a 28-day cycle

Population: patients with relapsed or refractory iNHL disease who were previously treated with at least 2 lines of systemic antineoplastic therapy including at least 1 anti-CD20 monoclonal antibody-containing therapy and an alkylating agent or lenalidomide

Variable: Objective response (i.e., best overall response of complete response or partial response) based on IRC assessment per Lugano criteria

Summary measure (population-level summary): overall response rate, the proportion of subjects achieving overall response

Handling Strategies for the Intercurrent Events for Primary Endpoint

Intercurrent Events	Handling Strategies for Addressing Intercurrent Events
Premature discontinuation of study treatment	**Treatment policy strategy:** Ignore the intercurrent events and use all data regardless of discontinuation of study treatment in the derivation of the endpoint
Use of subsequent anti-lymphoma therapy	**While on treatment strategy:** Response after the intercurrent event is excluded from the derivation of the endpoint

Sample size

The Expansion Part of the trial was carried out within 3 cohorts in a 2-stage design. In the iNHL cohort, assuming a non-evaluable rate of 10%, 33 subjects with FL Grade 1-3A were enrolled in Stage 1. If the futility criteria were met (no more than 15 responders out of 30 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 95 subjects with FL Grade 1-3A were to be enrolled to Stage 2, along with up to 30 subjects with other types of iNHL (MZL and SLL). In total, up to 158 subjects were to be enrolled in iNHL.

The null hypothesis was that the ORR for the FL Grade 1-3A group was at most 50%, and the alternative hypothesis was that the ORR is at least 65%. With one sample binomial test, this provided approximately 90% power to reject the null hypothesis with a two-sided significance level of 0.05. The probability of futility at the end of Stage 1 was approximately 57% under the null and 6.5% under the alternative.

Randomisation

NA; no control group is included in Study GCT3013-01, all included patients were planned to receive epcoritamab.

Blinding (masking)

NA; Study GCT3013-01 is an open label study.

Statistical methods

Analysis Populations:

Analysis sets in this study are defined as follows:

- **Enrolled subjects:** All subjects who signed the informed consent form.
- **Full Analysis Set (FAS):** All enrolled subjects who have been exposed to at least one dose of epcoritamab.
- **Modified Full Analysis Set (mFAS)**: The initial 100 consecutively treated subjects with FL. All responders would have had approximately 12 months follow-up from their initial response date or discontinued earlier by the planned cutoff date; therefore, this analysis set provides sufficient data to assess the durability of response in the target population.
- **Safety Analysis Set (SAF):** All enrolled subjects who have been exposed to at least one dose of epcoritamab, which is the same as FAS.
- **Response Evaluable Set (RES**): All subjects in the FAS with measurable disease at baseline, and either at least 1 post-baseline disease evaluation or have died within 60 days of first dose without post-baseline disease assessment.
- **Per Protocol Analysis Set (PP):** All subjects in the FAS with measurable disease at baseline and no important protocol deviations.
- **Pharmacokinetic Analysis Set**: All subjects in the FAS with at least one evaluable on-treatment PK sample collected.

- **Immunogenicity Analysis Set (IAS):** All subjects in the FAS with an evaluable baseline anti-drug antibody (ADA) sample, and at least one evaluable on-treatment ADA sample.
- **PRO Analysis Set:** All subjects in the FAS with a baseline and at least one post-baseline PRO score. All PRO analyses were based on the FAS. For analyses relating to changes from baseline, the PRO analysis set was used.

Efficacy:
Primary analysis for the Expansion Part of this trial was based on IRC-assessed ORR determined by Lugano criteria in the FAS.

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

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

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 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 and mFAS.

Other key secondary efficacy endpoints included DOR, CR rate, DOCR, PFS, TTR, TTCR, OS, TTNT, and rate of MRD negativity.

PFS is defined as the time from Day 1 of Cycle 1 to first documented PD or death due to any cause, whichever occurs earlier. PFS will be derived for all patients and presented graphically as well as summarized using survival analysis methods: distribution functions will be estimated using Kaplan-Meier technique. PFS was censored at the date of the last disease assessment prior to start of subsequent anti-lymphoma therapy in the primary definition (in the secondary definition, it was not); for both definitions patients who do not have disease progression and are alive are censored at clinical cutoff and are censored at last non-missing assessment if there are two or more missed assessment. If there is no post-baseline tumour assessment for an alive patient, PFS was censored on first dosing date. Date of PD was defined as the earliest date of documented progression after which there was no more PR or CR assessment.

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. DOR will be analyzed using the same statistical methodology as PFS. The date of PD is defined as the earliest date of documented progression after which there is no more PR or CR assessment. The (primary) definition of DOR that was used for the main analysis, accounted for subsequent anti-lymphoma therapy and censors DOR at the last adequate tumour assessment on or prior to the date of subsequent anti-lymphoma therapy. The secondary definition of DOR did not account for subsequent anti-lymphoma therapy.

Time to next anti-lymphoma therapy (TTNT) is defined as the time from Day 1 of Cycle 1 to first recorded administration of subsequent anti-lymphoma therapy or death due to any cause, whichever occurs earlier. In particular, death to other reasons than disease progression are censored and stem

cell transplant after response to epcoritamab was not considered subsequent anti-lymphoma therapy. TTNT was analyzed using the same statistical methodology as PFS.

OS is defined as the time from Day 1 of Cycle 1 to death. OS was analyzed using the same statistical methodology as PFS. If a patient is not known to have died, then OS was censored at the latest date the patient was known to be alive.

TTR is defined as the time from Day 1 of Cycle 1 to first documentation of objective tumour response (PR or better). It was derived for all patients achieving PR or CR. Analysis was based on response assessment by Lugano and LYRIC criteria, respectively.

The rate of MRD negativity (MRD-) is defined as the proportion of patients with at least one MRD- sample. Duration of MRD- is defined as the number of days from the first documentation of MRD- to the date of MRD status change (not MRD-). This was analyzed using the same statistical methodology as PFS.

Health-related quality of life analyses were conducted for all treated subjects who had baseline measurements. All PRO analyses were based on the FAS. For analyses relating to changes from baseline, the PRO analysis set was used.

Results of the FACT-Lym and EQ-5D-3L were summarized. Longitudinal and descriptive data analysis was used to evaluate PROs.

Analysis were conducted on the qualitative interviews to identify dominant trends and compare results across the interviews. Descriptive statistics of the quantitative data obtained during the interview (such as ratings of improvement) were computed and summarized to describe the patient experience.

Handling of Missing Data or Outliers

No imputation of missing data is planned for safety endpoints and PK endpoints. If outliers are detected, a robustness analysis where the outlier effect is reduced or eliminated may be considered.

No separate missing handling methods were explicitly defined for response endpoint (e.g. ORR and CR) so these were based on available assessment (but see the primary estimand; available assessments after treatment discontinuation were used, but not after subsequent anti-lymphoma therapy). Neither were missing handling methods for time-to-event endpoints (e.g. DoR) defined: these were handled by the censoring rules (censored at last available assessment) and most notably censored for start for new anti-lymphoma therapy.

Results

Participant flow

A total of 224 subjects were enrolled and 155 subjects received at least 1 dose of epcoritamab in the iNHL Expansion Part. A diagram showing the disposition of the 244 subjects screened in the iNHL expansion cohort is provided in Figure 9.

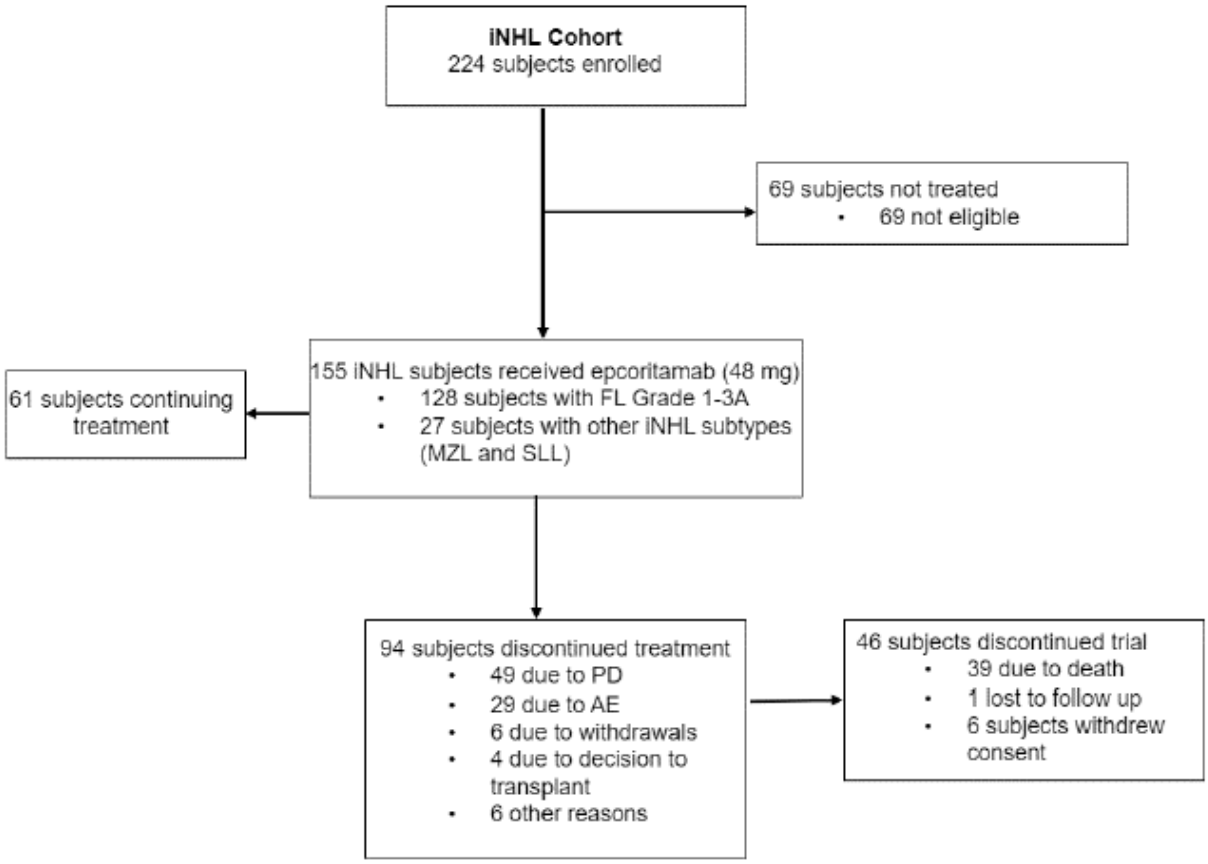
Of the 155 subjects who received at least 1 dose of epcoritamab, 128 subjects were diagnosed with FL Grade 1-3A and 27 subjects with other iNHL subtypes (i.e., MZL and SLL).

An enrolled subject was defined in the GCT3013-01 protocol as a subject who signed the ICF. Of a total of 224 subjects who signed informed consent, 69 (30.8%) were considered screen failures, which was defined as a subject who consented to participate in the study (signed ICF) but did not meet the protocol-defined eligibility criteria and therefore was not treated.

As of the data cutoff of 21 April 2023, 61 (39.4%) subjects in the iNHL expansion cohort were continuing on epcoritamab treatment. Overall, a total of 94 (60.6%) subjects had discontinued epcoritamab treatment. The most frequent primary reasons for treatment discontinuation were disease progression (49 [31.6%] subjects) and adverse event (29 [18.7%] subjects). A total of 46 (29.7%) subjects in the iNHL expansion cohort permanently discontinued the trial. The most common reason for trial discontinuation was death (39 [25.2%] subjects).

Of the 128 subjects with FL, 47 (36.7%) subjects were continuing on epcoritamab treatment. A total of 81 (63.3%) subjects with FL had discontinued epcoritamab treatment. The most frequent primary reasons for treatment discontinuation were disease progression (44 [34.4%] subjects) and adverse events (24 [18.8%] subjects). A total of 39 (30.5%) subjects with FL permanently discontinued the trial. The most common reason for trial discontinuation was death (34 [26.6%] subjects).

Figure 7: Subject Disposition – iNHL Cohort, Expansion Part



Data cutoff date: 21 April 2023

Table 7: Disposition of Subjects – iNHL Cohort, Expansion Part (Full Analysis Set)

	iNHL Cohort		
	FL 1-3A (N = 128)	**Other Subtypes[b] (N = 27)**	**Overall[c] (N = 155)**
Treated Subjects			
Ongoing trial treatment	**47 (36.7%)**	**14 (51.9%)**	**61 (39.4%)**
Discontinued study treatment	**81 (63.3%)**	**13 (48.1%)**	**94 (60.6%)**
Primary reason for study treatment discontinuation			
Progressive disease[a]	44 (34.4%)	5 (18.5%)	49 (31.6%)
Clinical progression	2 (1.6%)	1 (3.7%)	3 (1.9%)
Disease progression according to response criteria	42 (32.8%)	4 (14.8%)	46 (29.7%)
Adverse event	24 (18.8%)	5 (18.5%)	29 (18.7%)
Death	0	0	0
Withdrawal by subject[d]	3 (2.3%)	3 (11.1%)	6 (3.9%)
Decision to proceed with transplant	4 (3.1%)	0	4 (2.6%)
Other[e]	6 (4.7%)	0	6 (3.9%)
Subjects remain on trial	89 (69.5%)	20 (74.1%)	109 (70.3%)
Discontinued from trial	39 (30.5%)	7 (25.9%)	46 (29.7%)
Primary reason for trial discontinuation			
Death	34 (26.6%)	5 (18.5%)	39 (25.2%)
Lost to follow-up	1 (0.8%)	0	1 (0.6%)
Subject withdrew consent from trial	4 (3.1%)	2 (7.4%)	6 (3.9%)

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

b. Other subtypes include patients with marginal zone lymphoma (MZL) and small lymphatic lymphoma (SLL).

c. Overall refers to the total of FL 1-3A and other subtypes.

d. Withdrawal by subject includes 1 subject due to frequent hospitalizations, 2 subjects due to withdrawal of consent (no additional details), 1 subject due to unexpected hospitalizations and financial issues, 1 subject who achieved complete remission and no longer wished to continue in the trial, and 1 subject due to complete remission/chronic pain/possible relocation to a different state (Appendix 16.2.3.1).

e. 'Other' includes: 1 subject with complete response where reason was updated to maximum clinical benefit after the data cut-off, 1 subject in complete remission with recurrent infection and lack of compliance, 1 subject with an unfavorable benefit/risk ratio, 1 subject without evidence of response and considered not well enough to continue treatment, 1 subject with persistent COVID infection causing extended treatment delays and subsequent disease progression, and 1 subject with pre-existing MDS confirmed before screening who discontinued shortly after enrollment due to worsening of MDS (refer to Section 12.2.1.1 for further details).

Data cutoff date: 21 April 2023.

Recruitment

The Expansion Part of the trial began on 19 Jun 2020 (first subject first visit) and clinical data cut-off date was 31 April 2023. 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.

A total of 155 subjects in the iNHL Expansion Part received epcoritamab across 62 sites in Asia, Europe, North America, and Australia.

Conduct of the study

Protocol amendments

The original protocol (Version 2.0, 15 November 2017) had 11 versions/9 amendments. The protocol version 1.0 was dated 09 November 2017 but was not submitted.

A summary of key changes with each amendment include;

- Amendment 1-4 (between 18 Jan 2018 and 21 Jun 2019) were not applicable to the Expansion Part of the trial.
- Amendment 5 (4 Nov 2019); includes details regarding the Dose Expansion Part of the trial
    - Rationale, trial design, objectives/endpoints, inclusion/exclusion criteria, dose schedule and administration, statistical analysis, safety and other relevant sections in the protocol were updated to include information for the Dose 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 mBOIN design if an MTD was not reached.
    - Clarified that the end of treatment visit and safety follow-up visit were separate visits. Subjects discontinuing from treatment for any reason had a safety follow-up visit 4 weeks after the last dose of epcoritamab. If the subject started new anti-lymphoma therapy within 4 weeks of the last dose of epcoritamab, the safety follow-up visit was performed prior to starting new anticancer therapy. Renamed the post-safety follow-up contact to "survival status" rather than "overall survival."
    - 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 epcoritamab was increased to 60 days for the Dose Expansion Part of the trial.
    - Inclusion and exclusion criteria were revised for the Dose Expansion Part of the trial for clarity and based on Health Authority feedback.
    - In response to Health Authority feedback, added that subjects who received hepatitis C treatment that was intended to eradicate the virus could participate if hepatitis C RNA levels were undetectable.
    - Based on the assessment of the CRS incidence in the Dose Escalation Part of the ongoing trial, it was clarified that for the Expansion Part, hospitalization was only for 24 hours after the third (and first full dose) administration of epcoritamab. 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. It was added that based on the investigator's evaluation, the daily steroid dose requirements could be reduced from

100 mg to 80 mg to mitigate possible side effects from high-dose steroid administration.

- For the Dose Expansion Part, a bone marrow biopsy was mandated at screening to assess bone marrow involvement.
- Rationale for the R2PD to be used in the Dose Expansion Part was added.
- Qualitative interviews (patient-reported outcome assessment) were added to the patient-reported outcomes in the Dose Expansion Part.

- Amendment 7 (23 Sep 2020); A cohort of MCL subjects was added to the Dose Expansion Part of the trial. As a result, the trial design, inclusion/exclusion criteria, objectives and endpoints, statistical analysis and other relevant sections of the protocol were updated.
- Amendment 8 (22 Mar 2022); This protocol version was never implemented
- Amendment 9 (07 Jul 2022); A separate optimization part was added to the trial to explore alternative priming/intermediate epcoritamab dose levels in subjects with DLBCL, FL Grade 1-3A, and MCL. The goal of this part of the trial is to further optimize the epcoritamab dosing regimen to potentially lower the rate of ≥ Grade 2 CRS events and was added to align with HA feedback.

  Other Key changes;

  - Provided instructions for re-priming for all parts of the trial
  - Added recommendation for IV and oral fluids before and after each epcoritamab administration during the first cycle (i.e., the first 4 administrations of epcoritamab)
  - Clarified timing and choice of prophylactic corticosteroid (i.e., dexamethasone) treatment
  - The following inclusion criteria were updated:
    - Revised the minimum required ECOG PS for MCL subjects (i.e., must have ECOG PS < 2 in order to participate)
    - Revised lymphocyte count requirements for subjects with MCL
    - Added requirement for subjects to have life expectancy of > 3 months on SOC treatment
  - Added requirement for subjects to have access to intensive care management for treatment of CRS symptoms
  - Added instructions regarding SARS-CoV-2 vaccination during trial
  - Added treatment requirements for management of COVID-19 infections
  - Revised management instructions for CRS events
  - Revised management guidelines for ICANS based on ASTCT Guidelines
  - Added text to confirm that, in case of febrile neutropenia, the use of GCSF is mandatory
  - Inserted statement that only SAEs judged by the investigator as related to epcoritamab should be reported after the Safety Follow-up Visit

Protocol Deviations

Important protocol deviations for all subjects are summarized in Table 10.

At least one important protocol deviation occurred in 33 (21.3%) subjects in the iNHL expansion cohort. The majority of these deviations (20 of 33 subjects) was due to unauthorized collection of race/ethnicity data and analysis of tumour samples for RNA/DNA; these deviations were categorized under informed consent (14 subjects), regulatory (3 subjects), and data privacy (3 subjects); the remaining were due to dosing (8 [5.2%] subjects), enrollment criteria (4 [2.6%] subjects), and other (1 [0.6%] subjects).

Table 8: Important Protocol Deviations - iNHL Cohort, Expansion Part (Full Analysis Set)

	iNHL Cohort		
	FL 1-3A (N = 128)	**Other Subtypes (N = 27)**	**Overall[a] (N = 155)**
Number of Subjects with at least one important protocol deviation	29 (22.7%)	4 (14.8%)	33 (21.3%)
Informed Consent	13 (10.2%)	1 (3.7%)	14 (9.0%)
Dosing	7 (5.5%)	1 (3.7%)	8 (5.2%)
Enrollment Criteria	4 (3.1%)	0	4 (2.6%)
Data Privacy	3 (2.3%)	0	3 (1.9%)
Regulatory	2 (1.6%)	1 (3.7%)	3 (1.9%)
Other	0	1 (3.7%)	1 (0.6%)

a. Overall refers to the total of FL 1-3A and other subtypes.

Note: Percentages calculated based on number of subjects in Full Analysis Set.

Data cutoff date: 21 April 2023.

The COVID-19 pandemic had some impact on the conduct of the study, some protocol changes were implemented by protocol amendment and protocol deviations were closely monitored and captured. Control measures included inability to conduct visits according to schedule or use of virtual/remote visits due to lockdown or COVID-19 illness. Study visits were conducted differently for 9 (7.0%) subjects with FL due to COVID-19 control measure and for 26 (20.3%) subjects due to COVID-19 illness. Two (1.6%) subjects with FL had a dose of epcoritamab delayed due to COVID-19 control measure. There were no deaths due to COVID-19 control measures.

Baseline data

Demographic characteristics

The median age of subjects with FL was 65.0 years. Of note, 67 (52.3%) subjects were ≥ 65 years old, and 17 (13.3%) subjects were ≥ 75 years old. A total of 79 (61.7%) subjects were male, and 77 (60.2%) subjects were white. Race was not reported in 32.8% of subjects due to country-specific data protection laws and was reported as "other" in 1.6% of subjects. ECOG performance status at baseline was 0 for 70 (54.7%) subjects, 1 for 51 (39.8%) subjects, and 2 for 7 (5.5%) subjects. Twenty-two (17.2%) subjects had moderately impaired baseline renal function, and no subjects had severely impaired baseline renal function. Hepatic function at baseline was normal for 107 (83.6%) subjects (Table 11).

Table 9: Summary of Demographic Characteristics – iNHL Cohort, Expansion Part (Full Analysis Set)

Number of subjects, n (%)	iNHL Cohort		
	FL 1-3A (N = 128)	Other Subtypes (N = 27)	Overall[a] (N = 155)
Age at informed consent (years)			
Mean (std dev)	63.2 (11.20)	67.8 (11.72)	64.0 (11.38)
Median	65.0	70.0	65.0
Min, Max	39, 84	46, 86	39, 86
Age category			
<65 years	61 (47.7%)	10 (37.0%)	71 (45.8%)
65 years to < 75 years	50 (39.1%)	7 (25.9%)	57 (36.8%)
≥75 years	17 (13.3%)	10 (37.0%)	27 (17.4%)
Sex (at birth)			
Male	79 (61.7%)	15 (55.6%)	94 (60.6%)
Female	49 (38.3%)	12 (44.4%)	61 (39.4%)
Race			
White	77 (60.2%)	20 (74.1%)	97 (62.6%)
Asian	7 (5.5%)	3 (11.1%)	10 (6.5%)
Other	2 (1.6%)	0	2 (1.3%)
Not reported	42 (32.8%)	4 (14.8%)	46 (29.7%)
Weight (kg) at Baseline			
Mean (std dev)	80.0 (19.33)	74.1 (13.33)	78.9 (18.53)
Median	78.0	70.8	77.0
Min, Max	42.5, 171.9	54.0, 104.0	42.5, 171.9

Number of subjects, n (%)	iNHL Cohort		
	FL 1-3A (N = 128)	Other Subtypes (N = 27)	Overall[a] (N = 155)
ECOG performance status			
0	70 (54.7%)	12 (44.4%)	82 (52.9%)
1	51 (39.8%)	15 (55.6%)	66 (42.6%)
2	7 (5.5%)	0	7 (4.5%)
Baseline renal function (CrCl) (mL/min)			
Normal (≥90)	52 (40.6%)	11 (40.7%)	63 (40.6%)
Mildly impaired (60 to < 90)	54 (42.2%)	12 (44.4%)	66 (42.6%)
Moderately impaired (30 to < 60)	22 (17.2%)	4 (14.8%)	26 (16.8%)
Baseline hepatic function per NCI criteria			
Normal	107 (83.6%)	22 (81.5%)	129 (83.2%)
Mild dysfunction	21 (16.4%)	3 (11.1%)	24 (15.5%)
Moderate dysfunction	0	2 (7.4%)	2 (1.3%)

a. Overall refers to the total of FL 1-3A and other subtypes.

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

Baseline renal function calculated based on estimated creatine clearance using the Cockcroft Gault method.

Data cutoff date: 21 April 2023.

Demographic characteristics of the subjects with FL in first 100 consecutively treated subjects with FL (mFAS) were consistent with the characteristics of subjects with FL in FAS.

Baseline disease characteristics

Among subjects with FL, all but one subject (99.2%) had FL Grade 1-3A at study entry. One subject was enrolled as FL but was found to have transformed DLBCL after study entry. This subject is included in the FL FAS.

Forty-one subjects (32.0%) had FL Grade 3A disease; 109 (85.2%) of the subjects had advanced stage lymphoma (Ann Arbor Stage III and IV disease); 78 (60.9%) subjects had a FLIPI score ≥ 3. Thirty-three (25.8%) subjects had bulky disease at baseline (as assessed by IRC) with either a nodal or extranodal mass > 6 cm. Bone marrow involvement as assessed by the investigator was present in 38 (29.7%) subjects. Approximately two thirds of subjects (90 [70.3%]) were double refractory to an anti-CD20 and alkylating agent, and 67 (52.3%) subjects had progression of disease within 24 months (POD24) from any first line therapy. One hundred and one subjects (78.9%) were refractory to prior anti-CD20 therapy. The median time from initial diagnosis to first dose of epcoritamab was 5.8 years.

Table 10: Summary of Baseline Disease Characteristics – iNHL Cohort, Expansion Part (Full Analysis Set)

Number of subjects, n (%)	iNHL Cohort		
	FL 1-3A (N = 128)	Other Subtypes (N = 27)	Overall[c] (N = 155)
Disease type at trial entry			
FL Grade 1-3A	127 (99.2%)	0	127 (81.9%)
MZL	0	23 (85.2%)	23 (14.8%)
SLL	0	4 (14.8%)	4 (2.6%)
DLBCL	1 (0.8%)	0	1 (0.6%)
Histologic grade			
1	16 (12.5%)	0	16 (10.3%)
2	70 (54.7%)	0	70 (45.2%)
3A	41 (32.0%)	0	41 (26.5%)
Not applicable	1 (0.8%)	27 (100%)	28 (18.1%)
Median time from initial diagnosis to first dose[a] (years)	5.8	6.7	6.2

Number of subjects, n (%)	iNHL Cohort		
	FL 1-3A (N = 128)	Other Subtypes (N = 27)	Overall[c] (N = 155)
Ann Arbor stage at screening			
I	4 (3.1%)	0	4 (2.6%)
IE	1 (0.8%)	0	1 (0.6%)
II	14 (10.9%)	0	14 (9.0%)
IIE	0	0	0
III	30 (23.4%)	1 (3.7%)	31 (20.0%)
IIIE	1 (0.8%)	1 (3.7%)	2 (1.3%)
IIIS	1 (0.8%)	1 (3.7%)	2 (1.3%)
IIIE, S	0	0	0
IV	77 (60.2%)	24 (88.9%)	101 (65.2%)
FLIPI			
0-1	17 (13.3%)	0	17 (11.0%)
2	31 (24.2%)	0	31 (20.0%)
≥3	78 (60.9%)	0	78 (50.3%)
Unknown	1 (0.8%)	0	1 (0.6%)
Not applicable	1 (0.8%)	27 (100%)	28 (18.1%)
Bulky disease by IRC[b]			
≤ 6 cm	95 (74.2%)	22 (81.5%)	117 (75.5%)
> 6 cm	33 (25.8%)	5 (18.5%)	38 (24.5%)
POD24 status			
POD24 from any first line therapy	67 (52.3%)	11 (40.7%)	78 (50.3%)
POD24 from first time use of immunochemotherapy, regardless of line	66 (51.6%)	11 (40.7%)	77 (49.7%)
Prior anti-CD20 containing therapy	128 (100%)	27 (100%)	155 (100%)
Refractory[d]	101 (78.9%)	18 (66.7%)	119 (76.8%)
Double refractory to anti-CD20 and alkylating agent, regardless of two treatments being in the same or different treatment lines	90 (70.3%)	14 (51.9%)	104 (67.1%)
Bone marrow involvement at baseline by investigator	38 (29.7%)	20 (74.1%)	58 (37.4%)

Number of subjects, n (%)	iNHL Cohort		
	FL 1-3A (N = 128)	Other Subtypes (N = 27)	Overall[c] (N = 155)
Presence of constitutional symptoms			
Any constitutional symptom	16 (12.5%)	5 (18.5%)	21 (13.5%)
Night sweats	13 (10.2%)	5 (18.5%)	18 (11.6%)
Weight loss (> 10% over last 6 months)	6 (4.7%)	1 (3.7%)	7 (4.5%)
Fever	0	1 (3.7%)	1 (0.6%)
Extreme fatigue	3 (2.3%)	1 (3.7%)	4 (2.6%)

a. Time from diagnosis of disease recorded at time of study entry.

b. Bulky disease at baseline will be grouped by either nodal or extranodal mass > 6 cm, either nodal or extranodal mass ≤ 6 cm.

c. Overall refers to the total of FL 1-3A and other subtypes.

d. A subject is considered to be refractory if the subject experienced disease progression or stable disease as best response or disease progression within 6 months after therapy completion.

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

Data cutoff date: 21 April 2023.

Baseline disease characteristics of subjects in the mFAS were consistent with those of subjects with FL in the FAS.

Prior medications

Among subjects with FL, the median number of prior lines of systemic anti-lymphoma therapy was 3.0 (range: 2, 9); 40 (31.3%) subjects received 4 or more prior lines of therapies. Overall, all 128 subjects with FL had received prior alkylating agents and anti- CD20 therapy, 99 (77.3%) subjects received prior anthracycline therapy, and 40 (31.3%) subjects received prior lenalidomide. Twenty four (18.8%) subjects had a prior ASCT, with 10 (7.8%) subjects relapsing within 12 months of ASCT.

The median time from end of last line of therapy to first dose of epcoritamab was 5.2 months; 88 (68.8%) subjects were refractory to their last line of therapy prior to study entry, and 70 (54.7%) subjects were refractory to > 2 consecutive lines of prior therapy.

Table 11: Prior Therapy Related to the Disease Under Study – iNHL Cohort, Expansion Part (Full Analysis Set)

Number of subjects, n (%)	iNHL Cohort		
	FL 1-3A (N = 128)	Other Subtypes (N = 27)	Overall[c] (N = 155)
Prior systemic anti-lymphoma therapy	128 (100%)	27 (100%)	155 (100%)
Prior radiotherapy	33 (25.8%)	7 (25.9%)	40 (25.8%)
Prior surgery related to disease under study	13 (10.2%)	8 (29.6%)	21 (13.5%)
Prior stem cell transplant	24 (18.8%)	2 (7.4%)	26 (16.8%)
ASCT	24 (18.8%)	2 (7.4%)	26 (16.8%)
Subject relapsed ≤12 months after ASCT	10 (7.8%)	0	10 (6.5%)
Prior systemic therapy received			
Anti-CD20	128 (100%)	27 (100%)	155 (100%)
Anti-CD19	2 (1.6%)	0	2 (1.3%)
Alkylating Agents	128 (100%)	27 (100%)	155 (100%)
Anthracyclines	99 (77.3%)	14 (51.9%)	113 (72.9%)
Nucleotide	62 (48.4%)	9 (33.3%)	71 (45.8%)
Topo inhibitor	46 (35.9%)	2 (7.4%)	48 (31.0%)
PI3K inhibitor	29 (22.7%)	3 (11.1%)	32 (20.6%)
BCL2 inhibitor	1 (0.8%)	3 (11.1%)	4 (2.6%)
PolatuzumabV	3 (2.3%)	0	3 (1.9%)
CAR-T	6 (4.7%)	0	6 (3.9%)
Other	121 (94.5%)	25 (92.6%)	146 (94.2%)
Prior immunomodulatory therapy			
Lenalidomide	40 (31.3%)	1 (3.7%)	41 (26.5%)
Prior rituximab + lenalidomide drugs*			
Yes	27 (21.1%)	0	27 (17.4%)
No	101 (78.9%)	27 (100%)	128 (82.6%)

Number of subjects, n (%)	iNHL Cohort		
	FL 1-3A (N = 128)	Other Subtypes (N = 27)	Overall[c] (N = 155)
Number of prior lines of anti-lymphoma therapy			
n	128	27	155
Mean (Std Dev)	3.3 (1.59)	3.4 (1.45)	3.4 (1.57)
Median (Min, Max)	3.0 (2, 9)	3.0 (2, 7)	3.0 (2, 9)
1, n (%)	0	0	0
2, n (%)	47 (36.7%)	8 (29.6%)	55 (35.5%)
3, n (%)	41 (32.0%)	10 (37.0%)	51 (32.9%)
≥4, n (%)	40 (31.3%)	9 (33.3%)	49 (31.6%)
Median time from end of last-line anti-lymphoma therapy to first dose (months)	5.2	8.3	5.4
Subjects refractory to ≥2 consecutive lines of prior anti-lymphoma therapy[a]	70 (54.7%)	10 (37.0%)	80 (51.6%)
Last-line systemic antineoplastic therapy	128 (100%)	27 (100%)	155 (100%)
Refractory[a]	88 (68.8%)	15 (55.6%)	103 (66.5%)
No response	48 (37.5%)	11 (40.7%)	59 (38.1%)
Relapsed within 6 months after therapy completion	40 (31.3%)	4 (14.8%)	44 (28.4%)
Relapsed[b]	40 (31.3%)	12 (44.4%)	52 (33.5%)

* Source: Table 14.1.1.3.

a. A subject is considered to be refractory if the subject experienced disease progression or stable disease as best response or disease progression within 6 months after therapy completion.

b. A subject is considered to be relapsed if the subject experienced disease progression >6 months after last treatment.

c. Overall refers to the total of FL 1-3A and other subtypes.

Note: Percentages calculated based on number of subjects in FAS, unless otherwise specified.

Data cutoff date: 21 April 2023.

Prior therapies in subjects in the mFAS were comparable to those of subjects with FL in the FAS.

Concomitant medication

All subjects with FL except one (127 [99.2%]) received at least 1 concomitant medication. Paracetamol and sulfamethoxazole/trimethoprim were the most used concomitant medications (> 50% of subjects).

Among subjects with FL, 25 (19.5%) subjects had at least 1 on-treatment transfusion: 17 (68.0%) subjects had packed red blood cells transfusions, 6 (24.0%) subjects had platelet transfusions, 1 (4.0%) subject had plasma transfusions, and 1 (4.0%) subject had whole blood transfusions.

Concomitant medications in subjects in the mFAS were comparable to that of medications received by subjects with FL in the FAS. On-treatment transfusions in subjects in the mFAS were similar to that of transfusions received by subjects with FL in the FAS.

Subsequent Anticancer Therapies

Subsequent anti-lymphoma therapies for all subjects are summarized in Table 14 .

Among subjects with FL, a total of 38 (29.7%) subjects went on to receive subsequent anti-lymphoma therapy. The most common subsequent systemic therapy received was rituximab (12 [9.4%] subjects). Eight (6.3%) subjects received subsequent CAR-T therapy and 2 (1.6%) subjects received subsequent radiotherapy. In addition, 6 (4.7%) subjects received a subsequent SCT; 5 of these subjects received allogenic SCT. Of note, 3 of these subjects did not have progression on epcoritamab treatment prior to receiving allogeneic SCT.

Table 12: Subsequent Anti-lymphoma Therapies – iNHL Cohort, Expansion Part (Full Analysis Set)

Number of subjects, n (%) ATC level 2/generic name	iNHL Cohort		
	FL 1-3A (N = 128)	Other Subtypes (N = 27)	Overall[a] (N = 155)
Subjects with any subsequent anti-lymphoma therapy	38 (29.7%)	3 (11.1%)	41 (26.5%)
Subjects who received subsequent radiotherapy	2 (1.6%)	0	2 (1.3%)
Subjects who received subsequent stem cell transplant	6 (4.7%)	0	6 (3.9%)
Allogeneic SCT	5 (3.9%)	0	5 (3.2%)
Subjects received subsequent CAR-T cell therapy	8 (6.3%)	1 (3.7%)	9 (5.8%)
Subjects who received subsequent systemic drug therapy	30 (23.4%)	2 (7.4%)	32 (20.6%)
Antineoplastic agents[b]	30 (23.4%)	2 (7.4%)	32 (20.6%)
Rituximab	12 (9.4%)	1 (3.7%)	13 (8.4%)
Cyclophosphamide	7 (5.5%)	1 (3.7%)	8 (5.2%)

a. Overall refers to the total of FL 1-3A and other subtypes.

b. Where incidence for FL was >5.0%.

Note: Percentages calculated based on number of subjects in Full Analysis Set.
Subjects are counted at most one time within each generic name, and at most one time per each ATC level.
Subsequent therapy is administered after study-drug discontinuation.

Data cutoff date: 21 April 2023.

Subsequent anti-lymphoma therapies for subjects with FL in mFAS were similar to those received by subjects with FL in FAS.

Numbers analysed

Efficacy analyses were performed on the FAS and for the FL1-3A cohort and the cohort with other subtypes. The FAS population included 155 iNHL patients; 128 patients with FL 1-3A and 27 with other subtypes.

Sensitivity analyses for the primary efficacy endpoint ORR based on IRS assessment determined by Lugano criteria, were also performed for the PP set (N=142; n=117 FL1-3A and n=25 other subtypes; subjects in the FAS with measurable disease at baseline and no important protocol deviations), RES (N=151;N=126 FL1-3A and N=25 with other subtypes; 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).

A sensitivity analysis to assess the impact of the COVID-19 pandemic on study outcomes has been conducted.

Outcomes and estimation

As of the data cutoff date of 21 April 2023, median duration of follow-up for DOR for FL patients in the expansion cohort was 14.8 months, the median duration of treatment was 8.3 months, and the median number of cycles of treatment initiated per subject was 8.0 cycles.

Primary endpoint

The primary endpoint of ORR based on IRC assessment determined by Lugano criteria with PET scans for all subjects in the iNHL expansion cohort are presented in Table 15.

The ORR (CR + PR) in subjects with FL was 82.0% (95% CI: 74.3, 88.3), with 80 (62.5%) and 25 (19.5%) subjects achieving best responses of CR and PR, respectively.

Table 13: Best Overall Response Based on IRC Assessment, Lugano Criteria - iNHL Cohort, Expansion Part (Full Analysis Set)

	iNHL Cohort		
	FL 1-3A (N = 128)	**Other Subtypes (N = 27)**	**Overall (N = 155)**
Overall Response Rate (ORR)[a]	**105 (82.0%)**	**23 (85.2%)**	**128 (82.6%)**
(95% CI)[b]	(74.3%, 88.3%)	(66.3%, 95.8%)	(75.7%, 88.2%)
Complete Response Rate (CRR)	**80 (62.5%)**	**17 (63.0%)**	**97 (62.6%)**
(95% CI)[b]	(53.5%, 70.9%)	(42.4%, 80.6%)	(54.5%, 70.2%)
Partial Response Rate (PRR)	**25 (19.5%)**	**6 (22.2%)**	**31 (20.0%)**
(95% CI)[b]	(13.1%, 27.5%)	(8.6%, 42.3%)	(14.0%, 27.2%)
Best Overall Response			
Complete Response (CR)	80 (62.5%)	17 (63.0%)	97 (62.6%)
Partial Response (PR)	25 (19.5%)	6 (22.2%)	31 (20.0%)
Stable Disease (SD)	5 (3.9%)	0	5 (3.2%)
Progressive Disease (PD)	13 (10.2%)	2 (7.4%)	15 (9.7%)
Not Evaluable (NE)	5 (3.9%)	2 (7.4%)	7 (4.5%)

a. CR + PR. Includes subjects who had a PR or CR after an assessment of PD or indeterminate response (i.e., pseudoprogression).

b. Based on the Clopper and Pearson method.

Data cutoff date: 21 April 2023.

Six subjects had one indeterminate response (IR -LYRIC) by IRC followed by PR or CR (by Lugano) at subsequent time points as assessed by IRC. These subjects were included in the primary analysis as well as in the analysis of IRC-based secondary endpoints, such as CR rate, DOR, DOCR, TTR, TTCR, and PFS. All 6 subjects had durable responses after IR and 4 subjects with evaluable/available MRD had an MRD negative time point in plasma prior to response by Lugano criteria.

Two subjects with FL achieved a sustained complete metabolic response (CMR) by IRC, with PR as BOR. Both subjects had bone marrow lymphoma involvement detected by a local bone marrow aspirate and/ or biopsy at screening; however, a confirmatory bone marrow aspirate or biopsy was not performed at the time of CMR.

The ORR in subjects in the mFAS (first 100 consecutively treated subjects with FL) was 83.0% (95% CI: 74.2, 89.8), with 62 (62.0%) and 21 (21.0%) subjects achieving best responses of CR and PR, respectively.

Updated ORR

Based on an updated clinical DCO of 16 October 2023 the primary efficacy endpoint of ORR based on IRC assessment determined by Lugano criteria was 82.8% (95% CI: 75.1, 88.9) in subjects with FL, with 81 (63.3%) and 25 (19.5%) subjects achieving best responses of CR and PR, respectively (Table 14).

Table 14: Best Overall Response based on IRC Assessment, Lugano Criteria GCT3013-01 Expansion Part – Subjects with FL in iNHL Cohort (Full Analysis Set)

	FL 1–3A (N = 128)
Best Overall Response	
Complete Response (CR)	81 (63.3%)
Partial Response (PR)	25 (19.5%)
Stable Disease (SD)	5 (3.9%)
Progressive Disease (PD)	13 (10.2%)
Not Evaluable (NE)	4 (3.1%)
Overall Response Rate (ORR)[a]	106 (82.8%)
(95% CI)[b]	(75.1%, 88.9%)
Complete Response Rate (CRR)	81 (63.3%)
(95% CI)[b]	(54.3%, 71.6%)
Partial Response Rate (PRR)	25 (19.5%)
(95% CI)[b]	(13.1%, 27.5%)

a. CR + PR

b. Based on the Clopper and Pearson method

Note: Percentages calculated based on number of subjects in Full Analysis Set.

Data cutoff date: 16 October 2023.

Source: Table 14.2.1.1.1

Secondary efficacy endpoints

Overall Response Rate by Investigator Assessment Determined by Lugano Criteria

ORR in subjects with FL was 82.8% (95% CI: 75.1, 88.9), with 84 (65.6%) and 22 (17.2%) subjects achieving best responses of CR and PR, respectively.

Sensitivity analyses for ORR based on investigator assessment (Lugano criteria) conducted for the PP and RES populations were consistent with the ORR for the FAS.

For subjects enrolled asFL (N=128), the concordance rate between IRC and investigator, was 94.5% (kappa 0.81; 95% CI: 0.68, 0.95).

ORR in subjects in the mFAS was 83.0% (95% CI: 74.2, 89.8), with 66 (66.0%) and 17 (17.0%) subjects achieving best responses of CR and PR, respectively. Among the subjects in the mFAS, concordance was (96.0% [kappa 0.86; 95% CI: 0.72, 0.99]).

Updated data per DCO 16 October 2023 showed ORR in subjects with FL was 82.8% (95% CI: 75.1, 88.9), with 84 (65.6%) and 22 (17.2%) subjects achieving best responses of CR and PR, respectively.

Duration of Response Determined by Lugano Criteria

The DOR based on IRC assessment as determined by Lugano criteria (primary definition) for all subjects are presented in Table 17. A Kaplan-Meier plot for DOR based on IRC assessment for all subjects is provided in Figure 10.

Among the subjects with FL who achieved PR or CR (n=105), the median follow-up for DOR analysis was 14.8 months (range: 0.0+, 27.2+). The median DOR was not reached (NR) (95% CI: 13.7, NR). The estimated percentage of subjects remaining in response at 12 and 18 months was 68.7%, and 58.4%, respectively.

Table 15: Duration of Response Based on IRC Assessment, Primary Definition, Lugano Criteria - iNHL Expansion Cohort (Full Analysis Set)

	iNHL Cohort		
	FL 1-3A (N = 128)	**Other Subtypes (N = 27)**	**Overall (N = 155)**
All Responders (PR or CR)			
Number of Responders	105	23	128
Number of Events	36 (34.3%)	7 (30.4%)	43 (33.6%)
Number of Censored	69 (65.7%)	16 (69.6%)	85 (66.4%)
Reason for censoring			
Clinical cutoff	58 (84.1%)	14 (87.5%)	72 (84.7%)
New anti-lymphoma therapy	7 (10.1%)	1 (6.3%)	8 (9.4%)
Lost to follow-up	1 (1.4%)	0	1 (1.2%)
Subject withdrew consent	2 (2.9%)	1 (6.3%)	3 (3.5%)
PD (or death) after ≥ 2 consecutive missed tumor assessments	1 (1.4%)	0	1 (1.2%)
DOR (months)			
Min, Max	0.0+, 27.2+	0.0+, 16.2+	0.0+, 27.2+
Median follow-up (95% CI) [a]	14.8 (10.0, 15.2)	9.9 (6.9, 14.9)	14.2 (9.9, 14.9)
25% quartile (95% CI) [b]	5.3 (3.3, 12.2)	9.7 (1.3, 16.1)	9.5 (3.4, 12.4)
Median (95% CI) [b]	NR (13.7, NR)	16.1 (9.7, NR)	21.4 (14.0, NR)
75% quartile (95% CI) [b]	NR (NR, NR)	NR (14.4, NR)	NR (NR, NR)

	iNHL Cohort		
	FL 1-3A (N = 128)	**Other Subtypes (N = 27)**	**Overall (N = 155)**
Estimate percentage of patients remaining in response (95% CI)[b]			
6-month	74.2% (64.3%, 81.8%)	90.9% (68.3%, 97.6%)	77.3% (68.7%, 83.9%)
9-month	71.7% (61.4%, 79.7%)	90.9% (68.3%, 97.6%)	75.2% (66.3%, 82.1%)
12-month	68.7% (58.0%, 77.3%)	74.4% (43.2%, 90.1%)	70.3% (60.6%, 78.1%)
15-month	58.4% (46.4%, 68.7%)	51.0% (18.7%, 76.3%)	58.2% (47.0%, 67.9%)
18-month	58.4% (46.4%, 68.7%)	NR (NR, NR)	55.0% (42.6%, 65.8%)
Complete Responders			
Number of Responders	80	17	97
Number of Events	17 (21.3%)	5 (29.4%)	22 (22.7%)
Number of Censored	63 (78.8%)	12 (70.6%)	75 (77.3%)
Reason for censoring			
Clinical cutoff	56 (88.9%)	11 (91.7%)	67 (89.3%)
New anti-lymphoma therapy	4 (6.3%)	0	4 (5.3%)
Lost to follow-up	1 (1.6%)	0	1 (1.3%)
Subject withdrew consent	2 (3.2%)	1 (8.3%)	3 (4.0%)
PD (or death) after ≥ 2 consecutive missed tumor assessments	0	0	0
DOR (months)			
Min, Max	0.5, 27.2+	6.9+, 16.2+	0.5, 27.2+
Median follow-up (95% CI) [a]	14.8 (10.0, 15.2)	14.2 (7.2, 15.2)	14.8 (9.9, 15.1)
Median (95% CI) [b]	NR (21.4, NR)	16.1 (9.7, NR)	NR (21.4, NR)
75% quartile (95% CI) [b]	NR (NR, NR)	NR (14.4, NR)	NR (NR, NR)

	iNHL Cohort		
	FL 1-3A (N = 128)	Other Subtypes (N = 27)	Overall (N = 155)
Estimate percentage of patients remaining in response (95% CI) [b]			
6-month	88.4% (78.9%, 93.8%)	100.0% (100.0%, 100.0%)	90.5% (82.5%, 94.9%)
9-month	86.8% (76.7%, 92.7%)	100.0% (100.0%, 100.0%)	89.2% (80.7%, 94.0%)
12-month	84.6% (73.6%, 91.3%)	81.8% (44.7%, 95.1%)	84.5% (74.4%, 90.8%)
15-month	73.6% (59.7%, 83.3%)	56.1% (19.5%, 81.5%)	71.2% (58.2%, 80.8%)
18-month	73.6% (59.7%, 83.3%)	NR (NR, NR)	67.3% (52.4%, 78.4%)

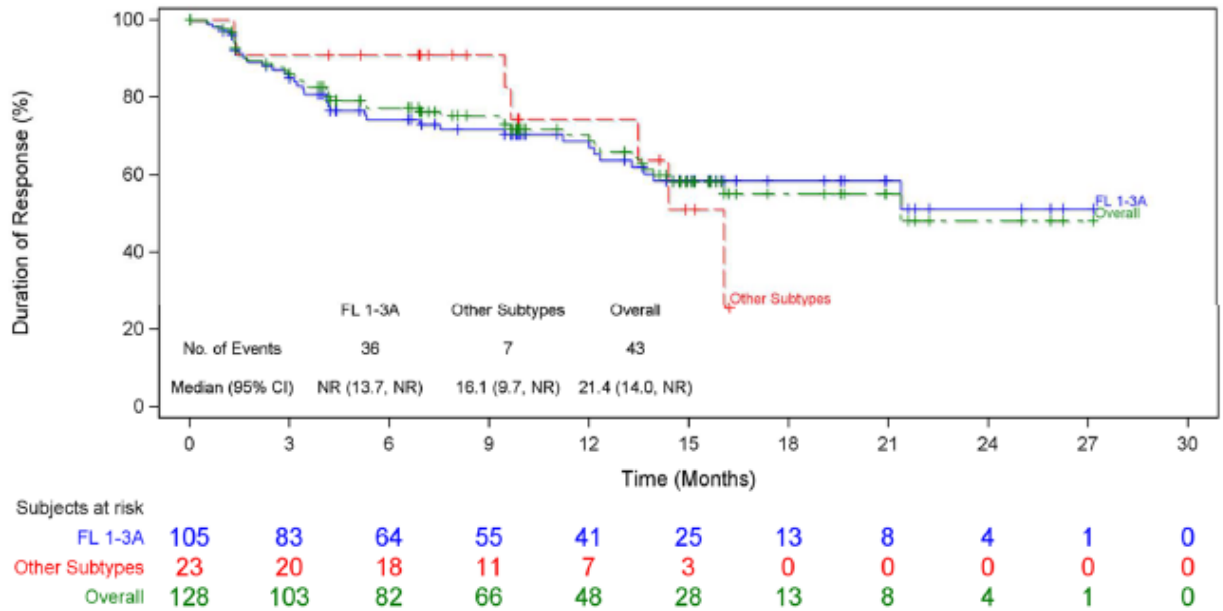
a. Based on reverse Kaplan-Meier estimate.

b. Based on Kaplan-Meier estimate.

Note: Symbol '+' indicated a censored value.

Data cutoff date: 21 April 2023.

Figure 8: Kaplan-Meier Plot of Duration of Response based on IRC Assessment, Primary Definition, Lugano Criteria - GCT3013-01 Expansion Part - Subjects in iNHL Cohort - Full Analysis Set



Data cutoff date: 21 April 2023.

For patients with FL, the median DOR by secondary definition, i.e. not censoring for new anticancer therapy, was reached at 21.4 months (95% CI: 13.3, NR). The 12-month estimate of patients remaining in response, using secondary definition, was 66.5% (95% CI: 55.9, 75.2).

For patients (FAS) with reported CR median DOCR was not reached (NR) (95% CI: 21.4, NR), after a median DOCR follow-up of 14.8 months (range: 9.9, 15.1). For FL patients who had a CR to epcoritamab treatment, median DOCR was not reached (NR) (95% CI: 21.4, NR), after a median DOCR follow-up of 14.8 months (95% CI 10.0, 15.2).

Results of addition analysis sets were in line with results for the FAS and FL analysis set.

Updated DOR

The DOR for subjects with FL based on the primary definition (accounting for subsequent anti-lymphoma therapy and censoring DOR at the last adequate tumour assessment on or prior to the date of subsequent anti-lymphoma therapy) and secondary definition (not accounting for subsequent anti-lymphoma therapy) are provided in Table 16.

The median DOR for all responders was per primary definition 23.6 months [95% CI: 13.8, NR] and per secondary definition 21.4 months [95% CI: 13.7, NR].

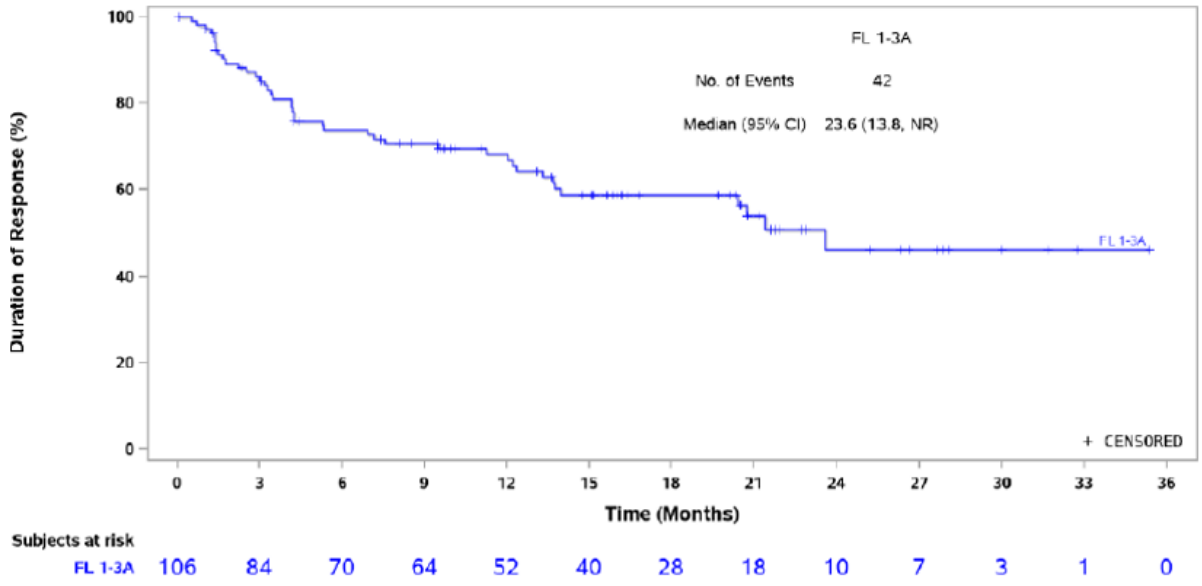
The median DOCR based on IRC Assessment, Lugano Criteria with the primary definition and secondary definition was NR.

Table 16: Duration of Response based on IRC Assessment, Lugano Criteria, Primary Definition – GCT3013-01 Expansion Part – Subjects with FL in iNHL Cohort (Full Analysis Set)

	FL 1–3A (N = 128)
Number of Responders (all responders [PR or CR])	106
Number of Events	42 (39.6%)
Number of Censored	64 (60.4%)
Reason for censoring	
Clinical cutoff[a]	51 (79.7%)
New anti-lymphoma therapy[a]	7 (10.9%)
Lost to follow-up[a]	2 (3.1%)
Subject withdrew consent[a]	3 (4.7%)
PD (or death) after ≥ 2 consecutive missed tumour assessments[a]	1 (1.6%)
DOR (months)	
Min, Max	0.0+, 35.4+
Median follow-up (95% CI)[b]	16.0 (15.1, 20.5)
25% quartile (95% CI)[c]	5.3 (3.3, 12.2)
Median (95% CI)[b]	23.6 (13.8, NR)
75% quartile (95% CI)[c]	NR (NR, NR)
Estimate percentage of patients remaining in response (95% CI)[c]	
3-month	85.2% (76.6%, 90.8%)
6-month	73.8% (64.0%, 81.4%)
9-month	70.6% (60.6%, 78.6%)
12-month	68.2% (57.9%, 76.5%)
15-month	58.8% (47.8%, 68.3%)
18-month	58.8% (47.8%, 68.3%)
21-month	53.9% (41.8%, 64.6%)

a. Denominators are based on the number of censored subjects.
b. Based on reverse Kaplan-Meier estimate.
c. Based on Kaplan-Meier estimate.
Note: Symbol '+' indicated a censored value.
Data cutoff date: 16 October 2023.

Figure 9: Kaplan-Meier Plot of Duration of Response Based on IRC Assessment, Lugano Criteria, Primary Definition – GCT3013- 01 Expansion Part – Subjects with FL in iNHL Cohort (Full Analysis Set)



Data cutoff date: 16 October 2023.

Source: Figure 14.2.1.9.1

Progression-free Survival Determined by Lugano Criteria

PFS based on IRC assessment (Lugano criteria) per the primary definition for all subjects is presented in table 19 and Figure 12.

Among subjects with FL, 55 (43.0%) subjects experienced a PFS event. The median PFS (primary definition), after a median follow-up of 16.1 months (range: 0.0+, 28.8+), was 15.4 months (95% CI: 10.9, NR). The estimated percentage of subjects remaining progression free at 15 and 21 months was 50.9 % and 49.4%, respectively.

Similar results for PFS based on the secondary definition (FAS) were observed.

Based on IRC assessment, 44 (44.0%) subjects in the mFAS experienced a PFS event (disease progression or death). The median PFS (primary definition), after a median follow-up of 16.6 months (range: 0.0+, 28.8+) was 22.8 months (95% CI: 12.6, NR). The estimated percentage of subjects remaining progression-free at 12 and 18 months was 61.3%, and 51.1%, respectively.

Table 17: Progression-Free Survival based on IRC Assessment, Lugano Criteria, Primary Definition - GCT3013-01 Expansion Part - Subjects in iNHL Cohort - Full Analysis Set

	iNHL Cohort		
	FL 1-3A (N = 128)	**Other Subtypes (N = 27)**	**Overall (N = 155)**
Number of Events	55 (43.0%)	10 (37.0%)	65 (41.9%)
Number of Censored	73 (57.0%)	17 (63.0%)	90 (58.1%)
Reason for censoring			
Clinical cutoff	58 (79.5%)	14 (82.4%)	72 (80.0%)
New anti-lymphoma therapy	7 (9.6%)	1 (5.9%)	8 (8.9%)
Lost to follow-up	1 (1.4%)	0	1 (1.1%)
Subject withdrew consent	2 (2.7%)	1 (5.9%)	3 (3.3%)
PD (or death) after ≥ 2 consecutive missed tumor assessments	2 (2.7%)	0	2 (2.2%)
No post-baseline assessments	3 (4.1%)	1 (5.9%)	4 (4.4%)
PFS (months)			
Min, Max	0.0+, 28.8+	0.0+, 18.1	0.0+, 28.8+
Median follow-up (95% CI)[a]	16.1 (11.3, 16.8)	11.1 (8.5, 16.8)	15.7 (11.3, 16.5)
25% quartile (95% CI)[b]	4.0 (2.7, 5.4)	10.9 (1.2, 16.0)	4.0 (2.7, 5.6)
Median (95% CI)[b]	15.4 (10.9, NR)	16.0 (11.1, NR)	16.0 (13.6, NR)
75% quartile (95% CI)[b]	NR (NR, NR)	18.1 (16.0, NR)	NR (NR, NR)
Estimate percentage of patients remaining progression free (95% CI)[b]			
6-month	64.5% (55.2%, 72.4%)	80.3% (58.9%, 91.3%)	67.3% (59.0%, 74.4%)
9-month	61.5% (52.0%, 69.7%)	80.3% (58.9%, 91.3%)	64.9% (56.4%, 72.2%)
12-month	59.3% (49.7%, 67.8%)	68.8% (44.6%, 84.1%)	61.2% (52.4%, 68.8%)
15-month	50.9% (40.5%, 60.4%)	59.0% (31.2%, 78.7%)	52.5% (42.8%, 61.2%)
18-month	49.4% (39.0%, 59.1%)	49.1% (21.4%, 72.1%)	49.9% (40.1%, 58.9%)
21-month	49.4% (39.0%, 59.1%)	NR (NR, NR)	46.5% (35.4%, 56.9%)

NR = Not reached

a. Based on reverse Kaplan-Meier estimate.

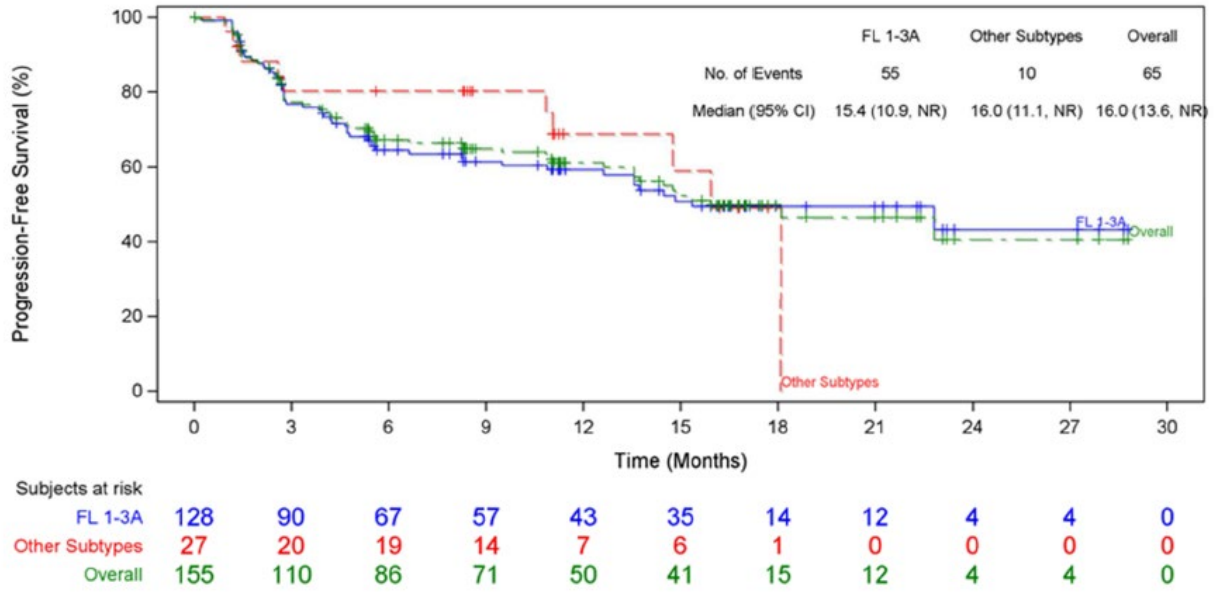
b. Based on Kaplan-Meier estimate.

Note: Symbol '+' indicated a censored value.

Data cutoff date: 21 April 2023.

Source: Table 14.2.1.12.1

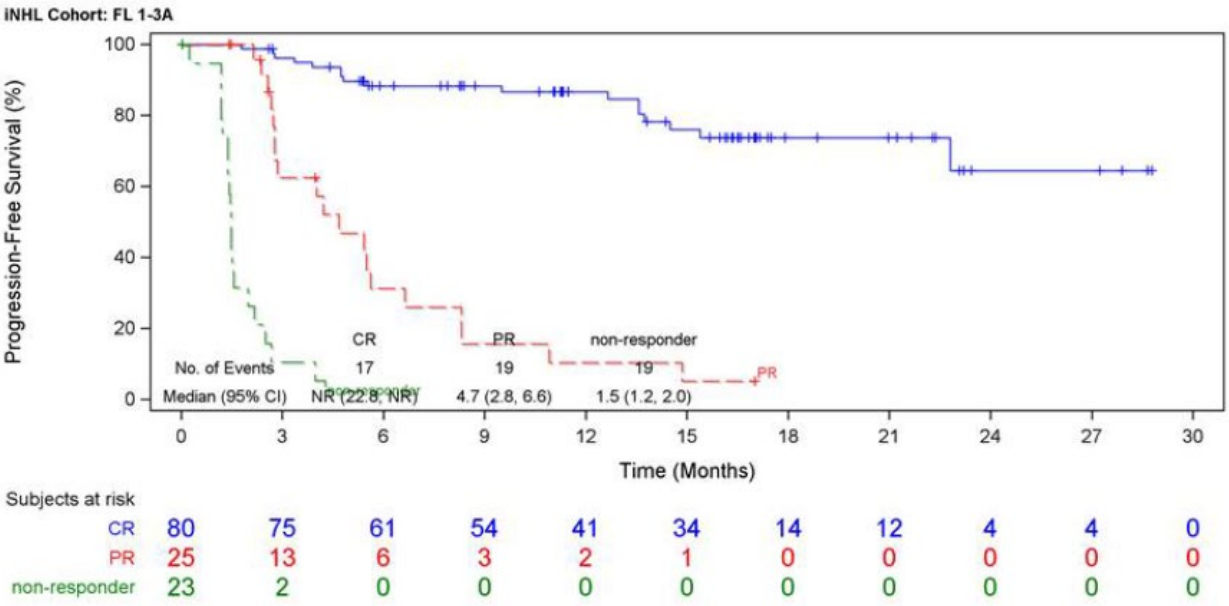
Figure 10: Kaplan-Meier Plot of Progression-Free Survival based on IRC Assessment, Lugano Criteria, Primary Definition - GCT3013-01 Expansion Part - Subjects in iNHL Cohort - Full Analysis Set



Data cutoff date: 21 April 2023.

Median PFS based on IRC was NR (95% CI: 22.8, NR) for FL subjects with CR. A longer median PFS was observed for FL subjects with PR (4.7 months [95% CI: 2.8, 6.6]) as compared to non-responders (1.5 months [95% CI: 1.2, 2.0]).

Figure 11: Kaplan-Meier Plot of Progression-Free Survival based on IRC Assessment, Lugano Criteria, Primary Definition by Best Overall Response - GCT3013-01 Expansion Part – Subjects in iNHL Cohort –FL1-3A Cohort



Based on investigator assessment, 59 (46.1%) subjects with FL, experienced a PFS event (disease progression or death). The median PFS (primary definition), after a median follow-up of 16.2 months

(range: 0.0+, 28.8+), was 13.7 months (95% CI: 8.8, NR). The estimated percentage of subjects remaining progression free at 12 and 18 months was 56.4% and 45.7% respectively.

Concordance rate for PFS assessment (primary definition) between IRC and investigator (Lugano criteria) was 93.8% (kappa 0.87; 95% CI; 0.79, 0.96).

With the updated DCO 16 October 2023 median PFS based on IRC by the primary definition was 15.4 months (95% CI: 10.9, NR) and by the secondary definition 15.1 months (95% CI: 8.3, 24.9). Estimated percentage of subjects remaining in response at 12 and 18 months of 57.5% and 47.9%, respectively.

Time to Response and Time to Complete Response Determined by Lugano Criteria

For subjects with FL, the median TTR based on IRC assessment was 1.4 months (range: 1.0, 3.0). The median TTCR based on IRC assessment was 1.5 months (range: 1.2, 11.1). This correlates to the first postbaseline disease assessment, indicating response was generally achieved early with epcoritamab treatment.

The median TTR and TTCR based on IRC assessment were both 1.4 months (range: 1.0, 3.0 and range:1.2, 11.1, respectively). These results were consistent with TTR and TTCR in the FAS.

With the updated DCO 16 October 2023, the median TTR for subjects with FL based on IRC assessment was 1.4 months (range: 1.0, 3.0) and the median TTCR based on IRC assessment was 1.5 months (range: 1.2, 11.1).

LYRIC Evaluation of Efficacy Endpoints based on IRC Assessment

- ORR per LYRIC in subjects with FL was 82.0% (95% CI: 74.3, 88.3), with 80 (62.5%) and 25 (19.5%) subjects achieving best responses of CR and PR, respectively. ORR as assessed by LYRIC was similar to ORR as assessed by Lugano.
- The median DOR in subjects with FL who had achieved PR or CR (N=105) based on IRC assessment (LYRIC) was NR (95% CI: 14.0, NR). The estimated percentage of subjects remaining in response at 12 and 18 months was 73.6% and 62.5%, respectively. The median DOR as assessed by LYRIC was similar to DOR as assessed by Lugano.
- The median DOCR in subjects with FL who had achieved CR (N=80) based on IRC assessment (LYRIC) was NR (95% CI: NR, NR). The estimated percentage of subjects remaining in complete response at 12 and 18 months was 81.9% and 71.9%, respectively. The median DOCR as assessed by LYRIC was similar to DOCR as assessed by Lugano.
- The median PFS (primary definition) in subjects with FL when assessed with LYRIC was NR (95% CI: 13.7, NR). The estimated percentage of subjects remaining progression-free at 12 and 18 months was 65.9% and 54.9%, respectively. The median PFS (secondary definition) when assessed with LYRIC was NR (95% CI: 13.6, NR). The estimated percentage of subjects remaining progression free at 12 and 18 months was 63.3% and 52.7%, respectively.

Overall Survival

At the time of data cutoff, there were 34 (26.6%) subjects with FL who died, and 94 (73.4%) subjects with FL who were still alive. With a median OS follow-up of 17.4 months, the median OS was NR (95% CI: NR, NR). The estimated percentage of subjects who remained alive at 12 and 18 months was 81.1% and 70.2%, respectively. Among subjects with FL who had achieved CR (N=80), the median OS with a median follow-up of 17.3 months was NR (95% CI: NR, NR). The estimated percentage of subjects remaining alive at 12 and 18 months was 93.4% and 82.9%, respectively.

Among subjects in the mFAS, there were 31 (31.0%) subjects who died. Median OS, with a median follow-up of 20.2 months (range: 0.2, 30.1+), was NR (95% CI: NR, NR). The estimated percentage of these subjects remaining alive at 12 and 18 months was 79.8% and 69.0%, respectively.

For subjects in the mFAS who had achieved CR (n=62), the median OS with a median follow-up of 20.5 months (range: 1.8, 30.0+) was NR (95% CI: NR, NR). The estimated percentage of subjects remaining alive at 12 and 18 months was 91.9% and 81.6%, respectively. Results of OS subgroup analyses in the mFAS were comparable to those in the FAS.

At the time of the updated DCO (16 October 2023), there were 39 (30.5%) subjects with FL who died, and 89 (69.5%) subjects who were still alive. With a median OS follow-up of 22.9 months, the median OS was NR (95% CI: NR, NR). The estimated percentage of subjects who remained alive at 12 and 18 months was 81.9% and 71.2%, respectively.

Time to Next Anti-lymphoma Therapy

Among subjects with FL, 44 (34.4%) subjects experienced a TTNT event, and 84 (65.6%) subjects were censored. The median TTNT was NR. The estimated percentage of subjects not initiating subsequent therapy at 12 and 18 months was 66.4% and 63.3%, respectively. Similar results were observed in the FAS and mFAS as in FL patients.

As of the DCO of 16 October 2023 among subjects with FL, 47 (36.7%) subjects experienced a TTNT event, and 81 (63.3%) subjects were censored. The median TTNT was NR (95% CI: 26.5, NR). The estimated percentage of subjects not initiating subsequent therapy at 12 and 18 months was 66.3% and 62.4%, respectively.

Rate and Duration of MRD Negativity

MRD was assessed at protocol-specified time points using clonoSEQ next-generation sequencing assay (Adaptive Biotechnologies, Seattle, Washington, US). The SAP-defined main method for assessment of MRD negativity in FL subjects was using the PBMC analyte at a threshold of 10^{-6}.

The rate of MRD negativity at any timepoint in MRD evaluable subjects with FL (N=91) was 67.0% (95% CI: 56.4, 76.5). With a median follow-up of 8.1 months, the median duration of MRD negativity was 16.5 months (95% CI: 10.8, NR).

The rate of MRD negativity at any timepoint using the PBMC analyte at a threshold of 10-6 in MRD evaluable subjects with FL (n = 93) was 65.6% (95% CI: 55.0, 75.1) at DCO 16 October 2023.

Progression-free Survival and OS by MRD Status

Among MRD evaluable subjects with FL (N=91), PFS and OS was improved in subjects with FL who achieved MRD negativity compared to subjects with FL who had MRD positive status.

Consistent results were observed for PFS and OS by MRD status for subjects with FL in the mFAS; PFS was improved in subjects who achieved MRD negativity compared to subjects with FL who had MRD positive status. Similar results were observed with the data update at 16 October 2023.

Figure 12: Kaplan-Meier Plot of PFS based on IRC Assessment, Lugano Criteria, Primary Definition by MRD Negativity Status per PBMC Assay with 1E-6 Cutoff - MRD Evaluable Set

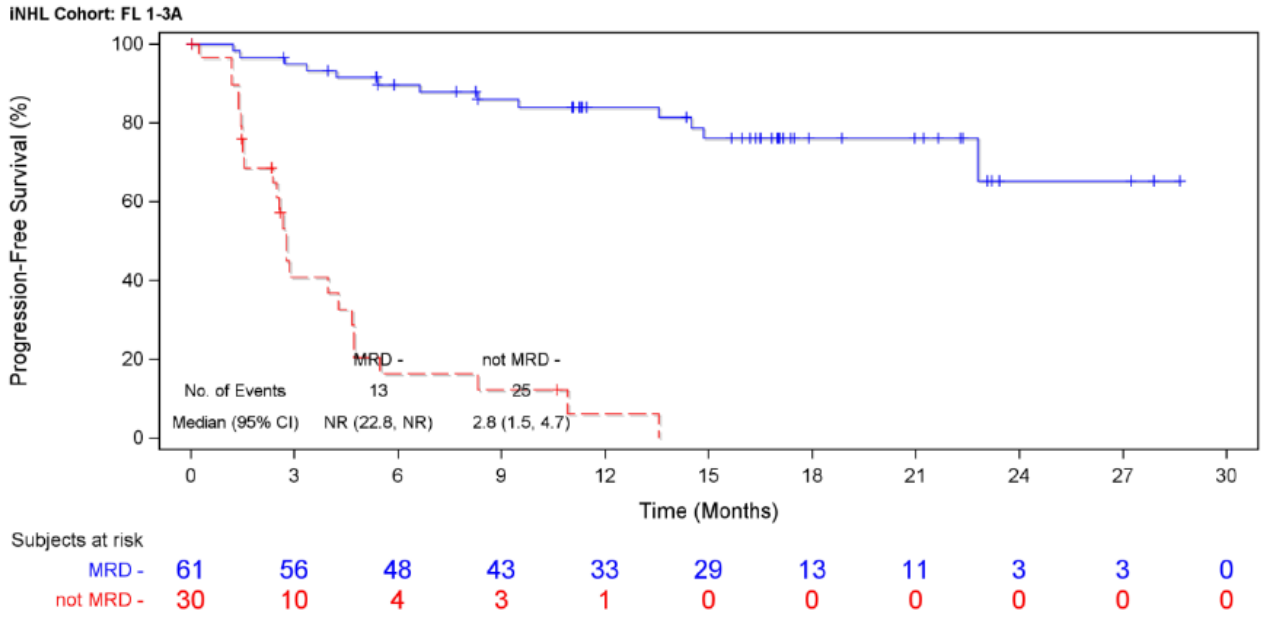
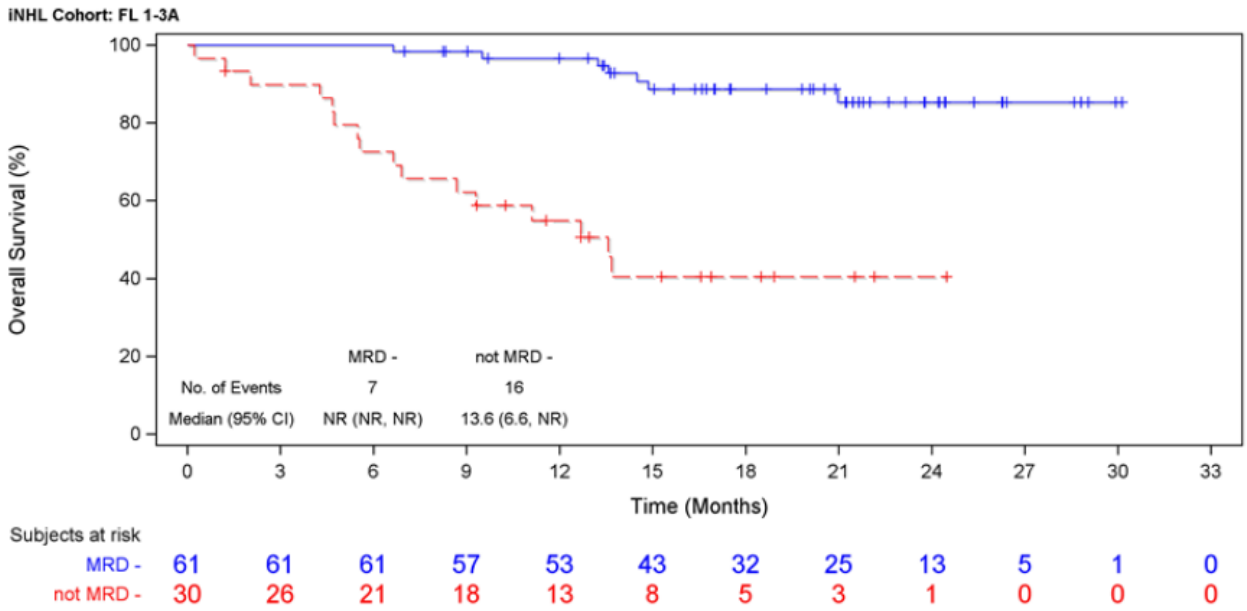


Figure 13: Kaplan-Meier Plot of OS based on IRC Assessment, Lugano Criteria, Primary Definition by MRD Negativity Status per PBMC Assay with 1E-6 Cutoff - MRD Evaluable Set



Quality of Life: Changes in Well-Being and General Health Status (EQ-5D-3L), Changes in Lymphoma Symptoms (FACT-Lym)

Based on PROs assessed by the FACT-Lym and EQ-5D, while on treatment, FL patients treated with epcoritamab reported no deterioration in the symptoms and quality of life (QoL) experience, consistent with their QoL being maintained.

The FACT-LYM assessment included, six questions from the FACT-Lym (P2 [body pain], BRM3 [fever], ES3 [night sweats], GP1 [lack of energy], BMT6 [tires easily], and C2 [weight loss]) that were considered related to key symptoms of lymphoma and were secondary endpoints for the Expansion Part of the trial. The compliance rate for the FACT-LYM PRO was >75% at most time points. In the FACT-LYM scores a substantial proportion of patients reported during treatment at least a one-category improvement of any one of the six key lymphoma symptoms (body pain, fever, night sweats, lack of energy, tires easily, and weight loss; each assessed using a five-point severity response scale ranging from "not at all" to "very much") without worsening in the other five symptoms, from baseline through Cycle 9 Day1 [C9D1].

Table 18: Proportion of FL 1-3A Subjects with Improvements in the 6 Key Lymphoma Symptoms - GCT3013-01 Expansion Part – PRO Analysis Set

Symptom and Subjects Reporting the Symptom at Baseline	Percent of Subjects with at Least a One Category Improvement in the Corresponding Symptoms Without Worsening in any of the Other Symptoms, From Baseline Through C9D1							
	C2D1	C3D1	C4D1	C5D1	C6D1	C7D1	C8D1	C9D1
Body pain [P2], (n=76)	65.2% (n=45/69)	50.0%	50.9%	49.0%	62.7%	61.0%	48.6%	52.6% (n=20/38)
Fever [BRM3], (n=12)	54.5% (n=6/11)	66.7%	70.0%	75.0%	71.4%	100%	100%	100% (n=2/2)
Night sweats [ES3], (n=48)	72.1% (n=31/43)	64.1%	89.5%	78.8%	85.7%	84.0%	80.0%	87.5% (n=21/24)
Lack of energy [GP1], (n=84)	32.9% (n=25/76)	41.8%	35.6%	34.0%	44.2%	40.0%	45.0%	46.2% (n=18/39)
Tire easily [BMT6], (n=90)	32.9% (n=27/82)	48.6%	42.2%	44.4%	52.6%	47.7%	52.3%	55.8% (n=24/43)
Weight loss [C2], (n=31)	44.4% (n=12/27)	65.2%	83.3%	87.5%	88.9%	75.0%	92.9%	75.0% (n=12/16)

Data cutoff date: 21 April 2023.

Modest declines in the FACT-Lym scores were observed in EOT scores when patients progressed.

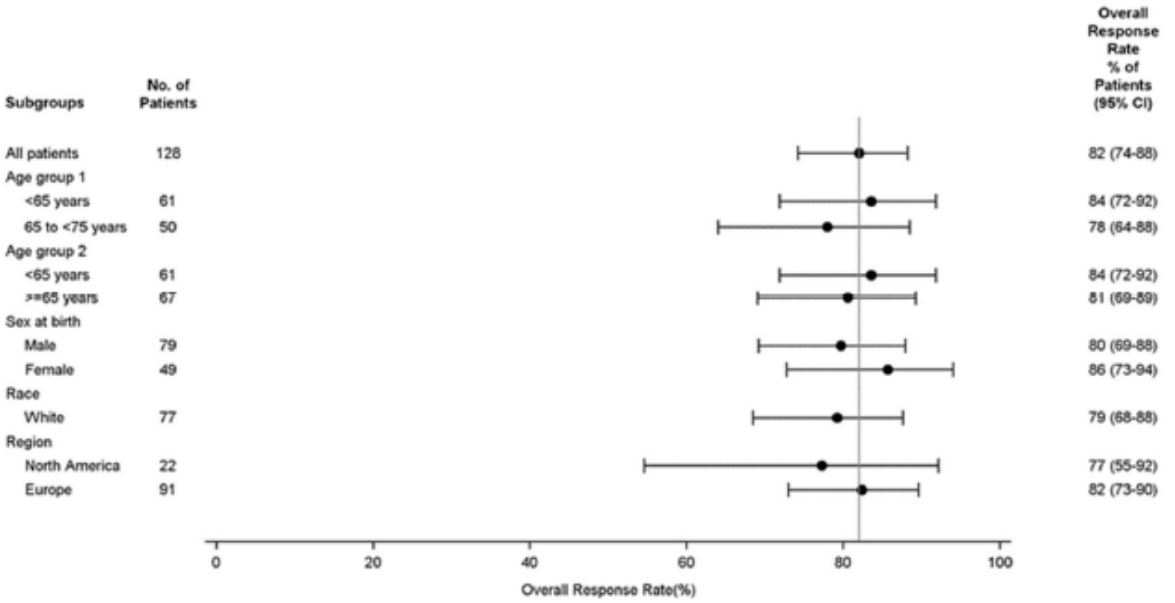
With the EQ-5D-3L Health Utility Scores, on treatment, mean (SD) EQ-5D utility scores improved from 0.776 (0.2574) at baseline (C1D1, N=122) to 0.827 (0.2015) at C9D1 (N=58), the final on-treatment time point measured. Among the subjects who later progressed and/or discontinued treatment (EOT), the mean (standard deviation) EQ-5D-3L scores remained comparable to the baseline at 0.773 (0.2336) (N=48).

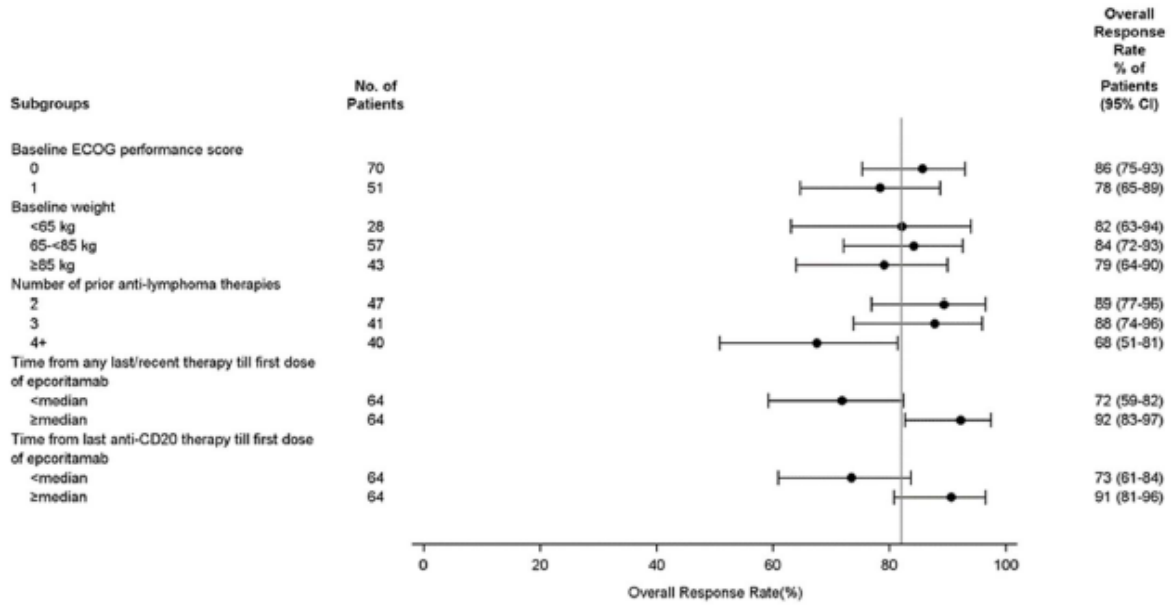
Ancillary analyses

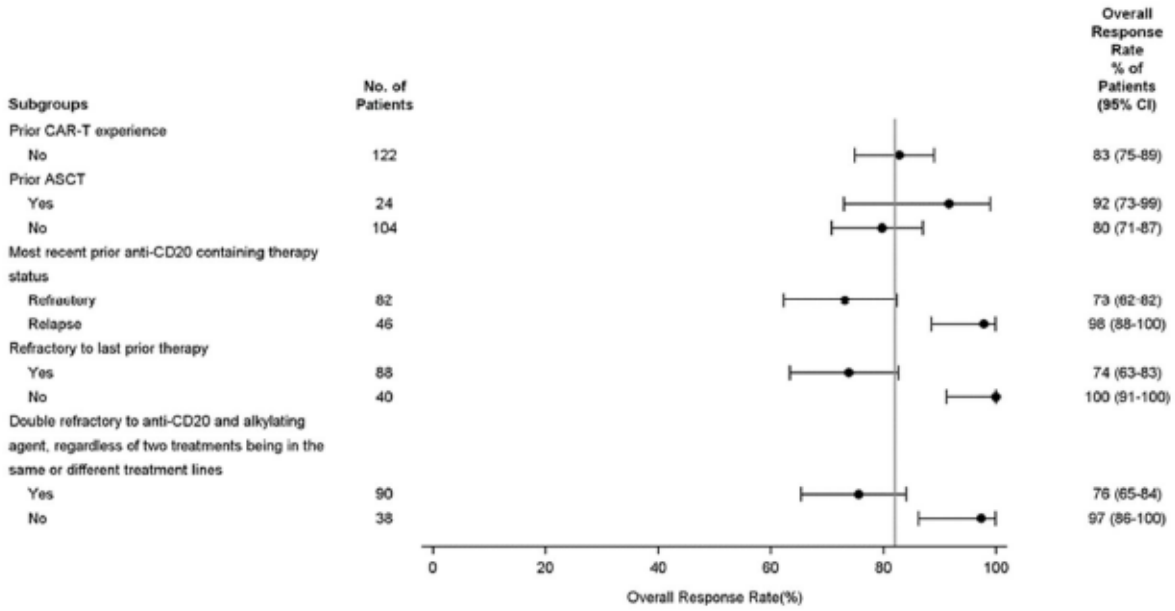
Subgroup analysis of Overall Response Rate

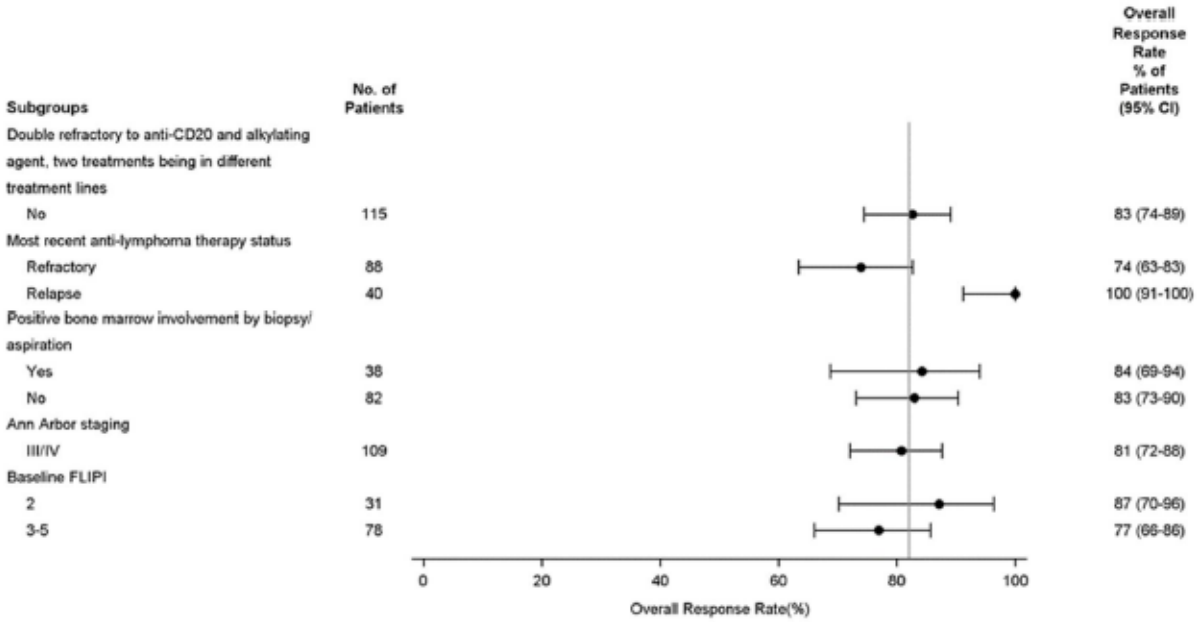
ORR in prespecified subgroups by IRC assessment, using the Lugano 2014 criteria, is presented in Figure 16 as a forest plot in for subjects with FL. For most subgroups, ORR was generally consistent with that of the ORR of all subjects with FL: 82.0% (95% CI: 74.3, 88.3). Subgroups results for the DCO 16 October 2023 were consistent.

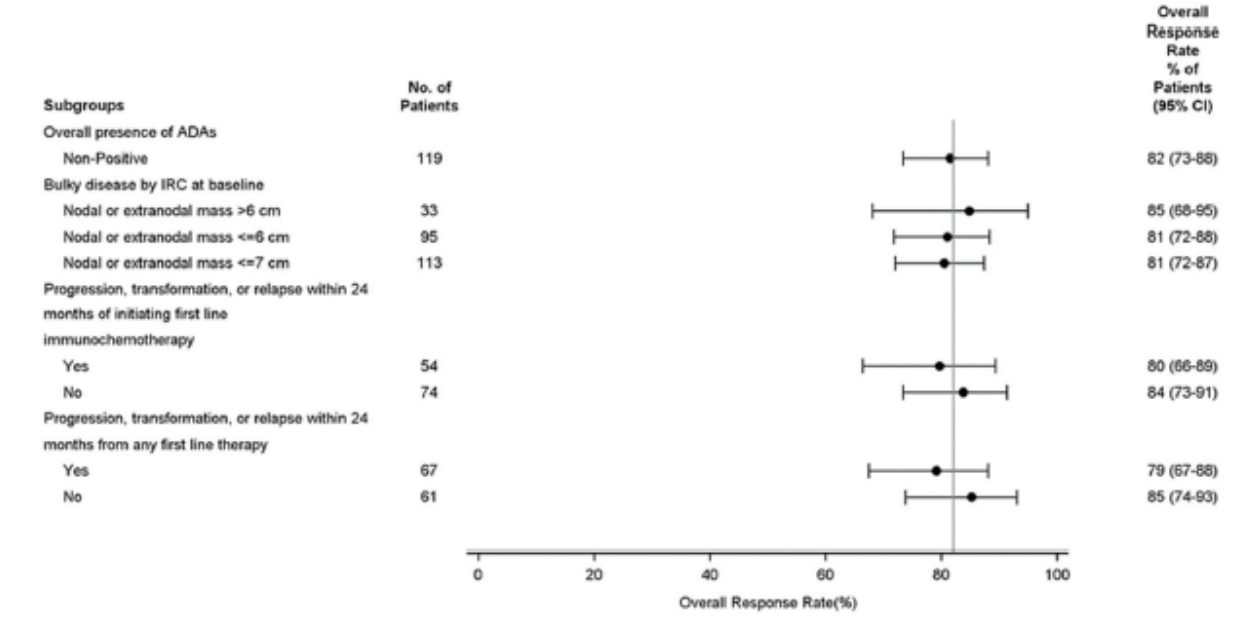
Figure 14: Forest Plot of Overall Response Based on IRC in Pre-Specified Subgroups, Lugano Criteria - GCT3013-01 Expansion Part FL 1-3A subjects in iNHL Cohort - Full Analysis Set

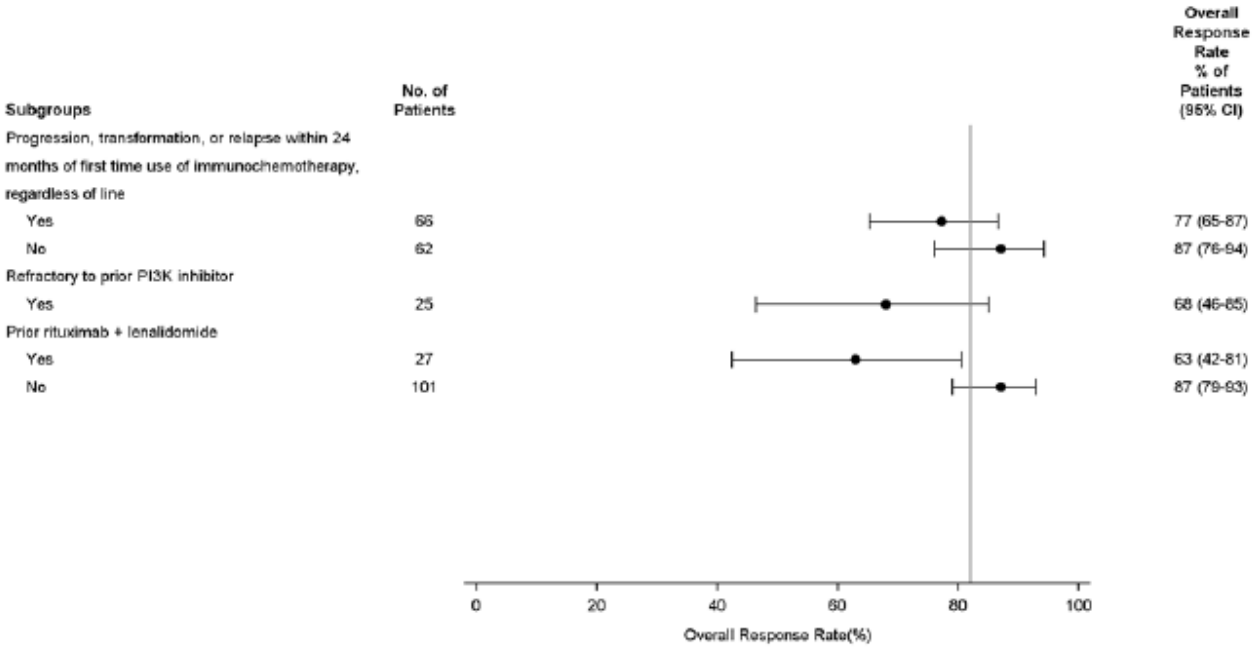





Subgroups
No. of Patients
Overall Response Rate % of Patients (95% CI)
Prior CAR-T experience
No 122 83 (75-89)
Prior ASCT
Yes 24 92 (73-99)
No 104 80 (71-87)
Most recent prior anti-CD20 containing therapy status
Refractory 62 73 (62-82)
Relapse 46 98 (88-100)
Refractory to last prior therapy
Yes 88 74 (63-83)
No 40 100 (91-100)
Double refractory to anti-CD20 and alkylating agent, regardless of two treatments being in the same or different treatment lines
Yes 90 76 (65-84)
No 38 97 (86-100)
0
20
40
60
80
100
Overall Response Rate(%)


Subgroups
No. of Patients
Overall Response Rate % of Patients (95% CI)
Double refractory to anti-CD20 and alkylating agent, two treatments being in different treatment lines
No 115 83 (74-89)
Most recent anti-lymphoma therapy status
Refractory 88 74 (63-83)
Relapse 40 100 (91-100)
Positive bone marrow involvement by biopsy/ aspiration
Yes 38 84 (69-94)
No 82 83 (73-90)
Ann Arbor staging
III/IV 109 81 (72-88)
Baseline FLIPI
2 31 87 (70-96)
3-5 78 77 (66-86)
0
20
40
60
80
100
Overall Response Rate(%)





Note: Subgroups with fewer patients (N < 20) are excluded.
Data cutoff date: 21 April 2023.

Subgroup Analysis of Duration of Response

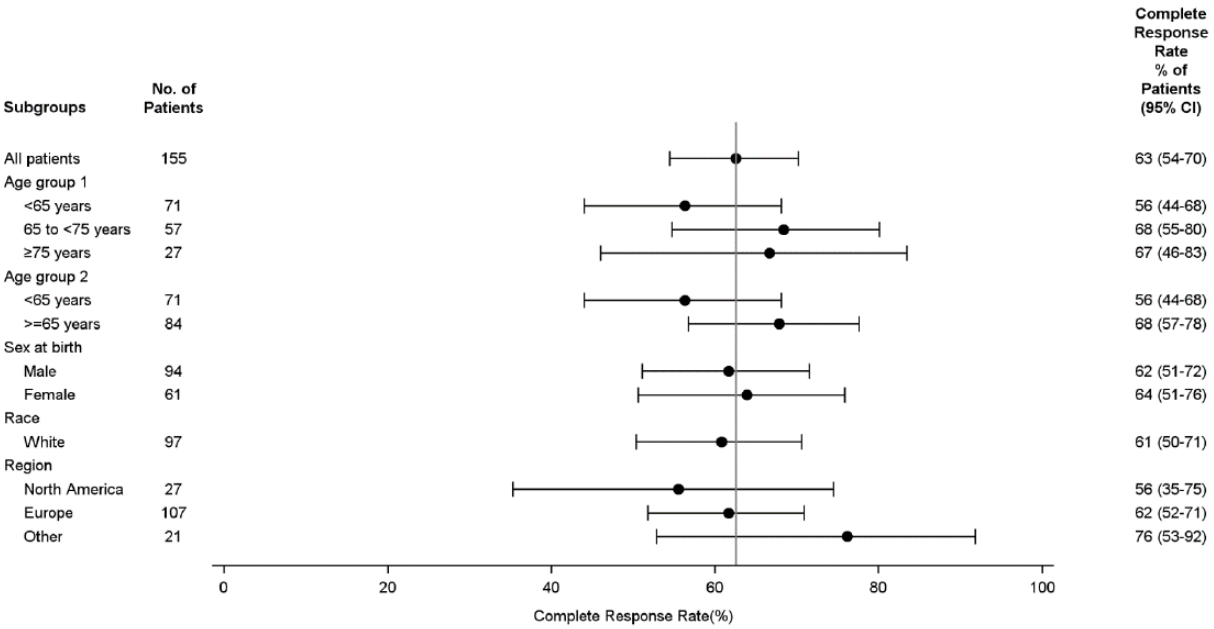
DOR in prespecified subgroups of subjects with FL was consistent with DOR results for the overall FL population (NR [95% CI: 13.7, NR]). Key observations from the subgroup analysis of DOR in subjects with FL are outlined below:

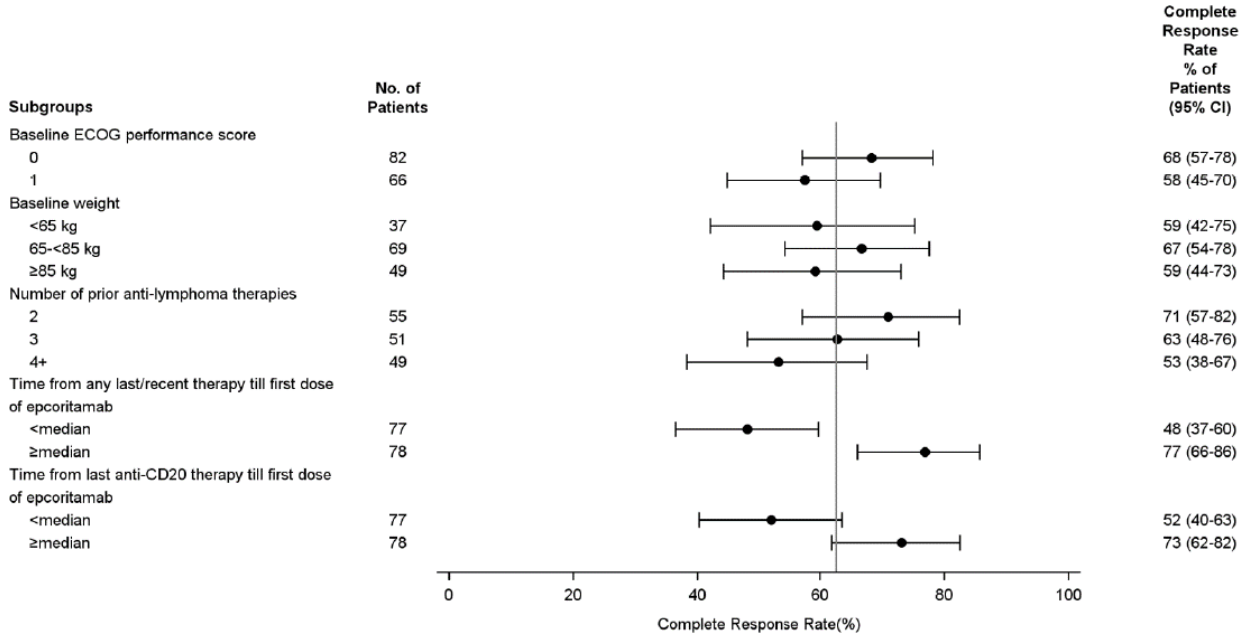
- The median DOR was NR (95% CI: NR, NR) in subjects aged <65 years (n=51) and 21.4 months (95% CI: 12.2, NR) in subjects aged ≥ 65 (n=54). In subjects 65 to <75 years (n=39), the median DOR was 21.4 months (95% CI: 13.7, NR).

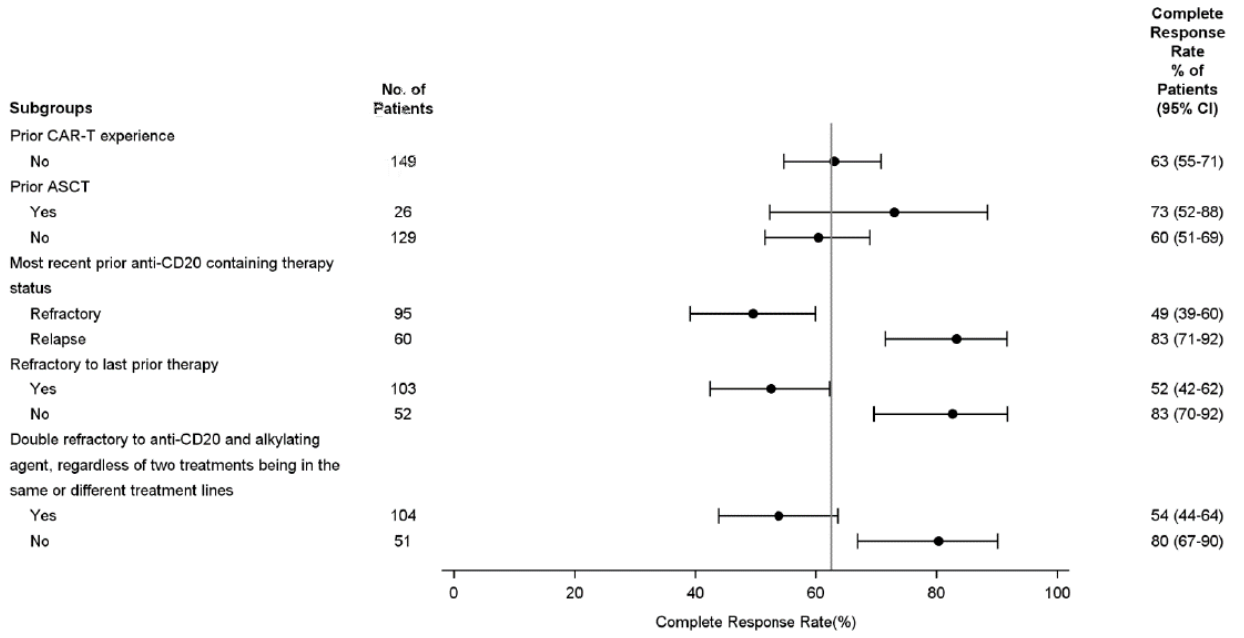
- The median DOR was NR (95% CI: 14.0, NR) in subjects with 2 prior lines (n=42), 21.4 months (95% CI: 12.0, NR) with 3 prior lines (n=36), and 13.7 months (95% CI: 6.9, NR) with ≥4 prior lines (n=27).
- The median DOR was NR (95% CI: 12.4, NR) in subjects double refractory to anti-CD20 and alkylating agent (n=68), and 21.4 months (95% CI: 12.0, NR) in subjects who were not double refractory (n=37).
- The median DOR was NR (95% CI: 12.0, NR) in subjects with baseline FLIPI score of 2 (n=27), 21.4 months (95% CI: 9.5, NR) in subjects with baseline FLIPI score of 3 – 5 (n=60).
- The median DOR was NR (95% CI: 5.3, NR) in subjects with nodal or extra nodal mass >6 cm (n=28), NR (95% CI: 13.7, NR) in subjects with nodal or extra nodal mass ≤ 6 cm (n=77).
- The median DOR was NR (95% CI: 13.3, NR) in subjects with POD24 (n=53), 21.4 months (95% CI: 9.5, NR) in subjects who were not POD24 (n=52).

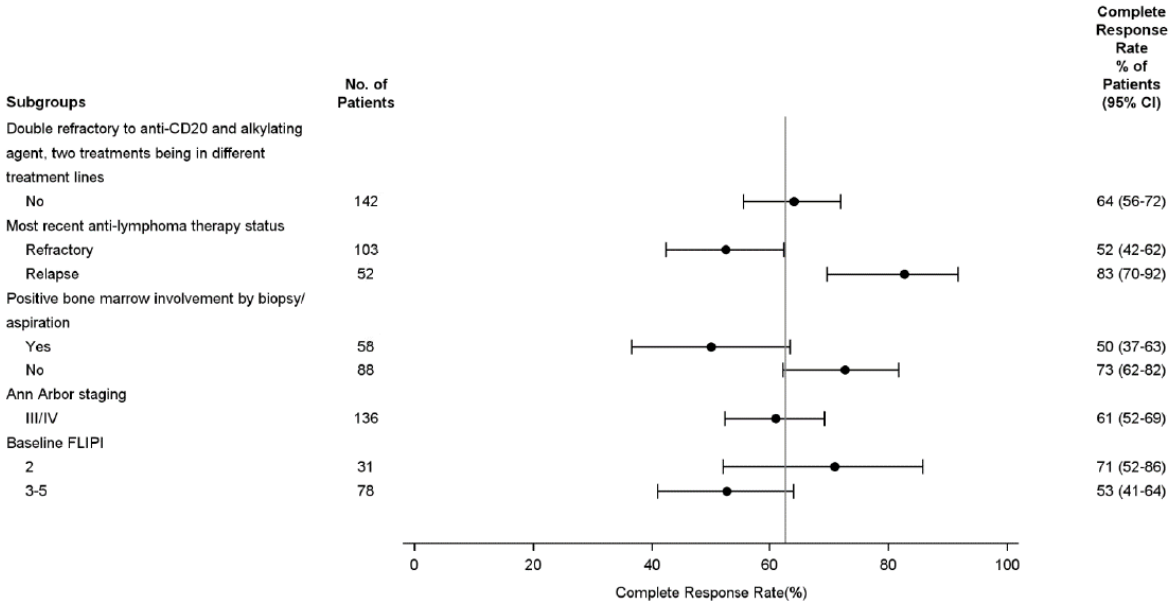
Complete Response Rate Determined by Lugano Criteria

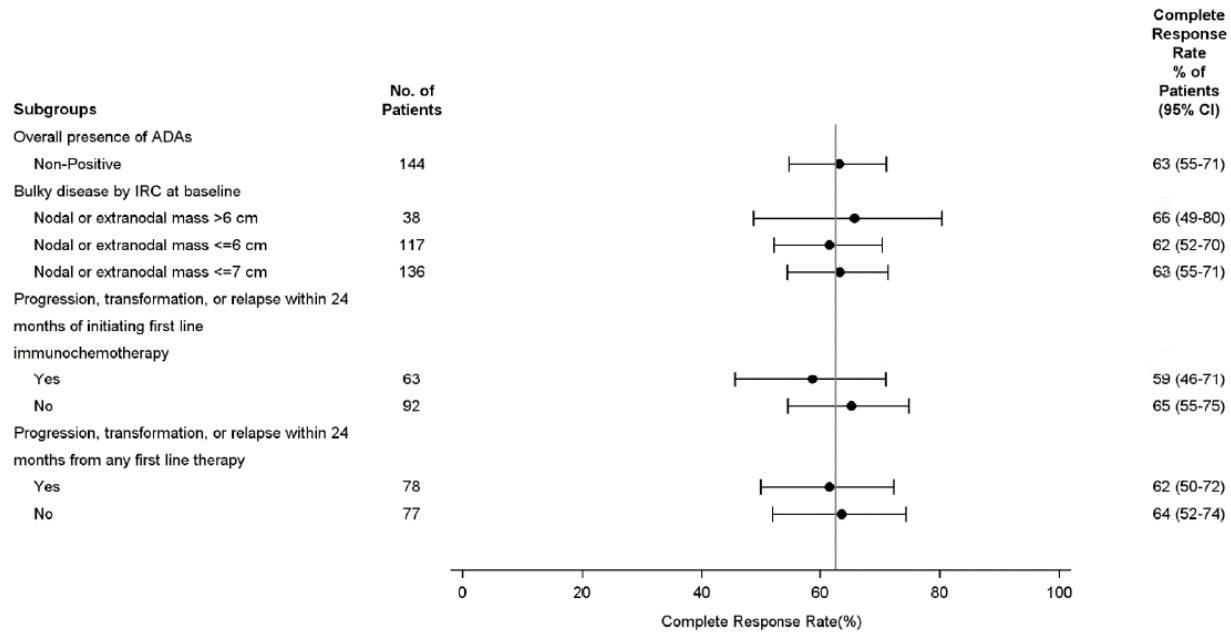
Figure 15: Forest Plot of Complete Response based on IRC Assessment in Pre-Specified Subgroups, Lugano Criteria GCT3013-01 Expansion Part - Subjects in iNHL Cohort - Full Analysis Set

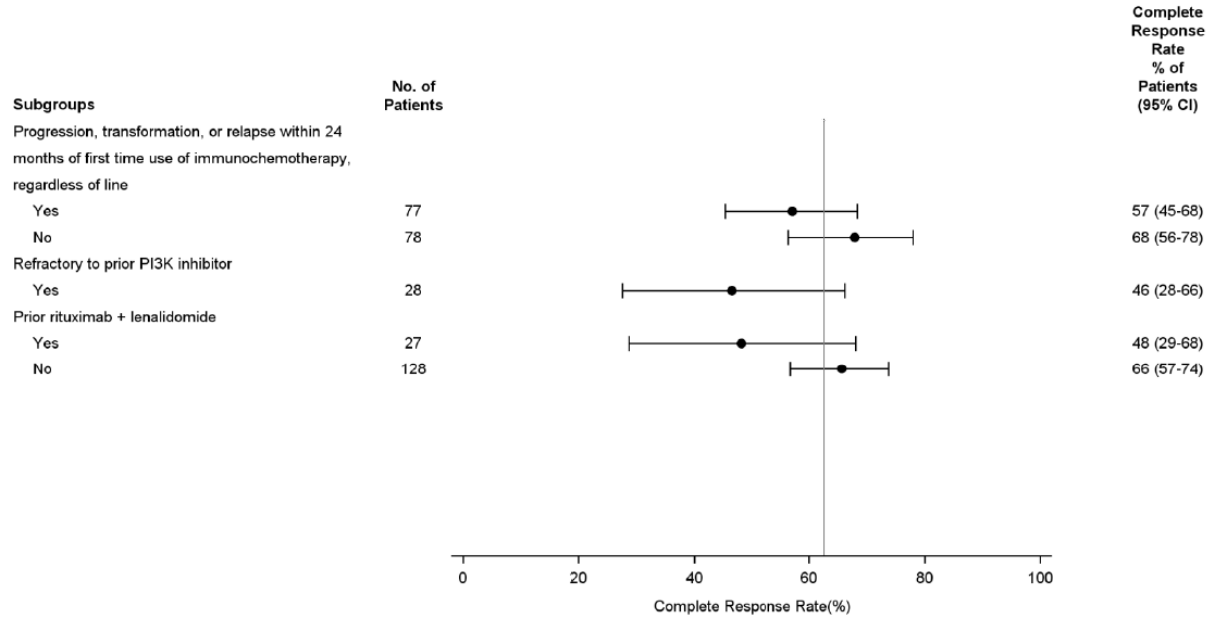



Subgroups
No. of Patients
Complete Response Rate % of Patients (95% CI)
Baseline ECOG performance score
0 82 68 (57-78)
1 66 58 (45-70)
Baseline weight
<65 kg 37 59 (42-75)
65-<85 kg 69 67 (54-78)
≥85 kg 49 59 (44-73)
Number of prior anti-lymphoma therapies
2 55 71 (57-82)
3 51 63 (48-76)
4+ 49 53 (38-67)
Time from any last/recent therapy till first dose of epcoritamab
<median 77 48 (37-60)
≥median 78 77 (66-86)
Time from last anti-CD20 therapy till first dose of epcoritamab
<median 77 52 (40-63)
≥median 78 73 (62-82)
0
20
40
60
80
100
Complete Response Rate(%)


Subgroups
No. of Patients
Complete Response Rate % of Patients (95% CI)
Prior CAR-T experience
No 149 63 (55-71)
Prior ASCT
Yes 26 73 (52-88)
No 129 60 (51-69)
Most recent prior anti-CD20 containing therapy status
Refractory 95 49 (39-60)
Relapse 60 83 (71-92)
Refractory to last prior therapy
Yes 103 52 (42-62)
No 52 83 (70-92)
Double refractory to anti-CD20 and alkylating agent, regardless of two treatments being in the same or different treatment lines
Yes 104 54 (44-64)
No 51 80 (67-90)
0
20
40
60
80
100
Complete Response Rate(%)


Subgroups
No. of Patients
Complete Response Rate % of Patients (95% CI)
Double refractory to anti-CD20 and alkylating agent, two treatments being in different treatment lines
No 142 64 (56-72)
Most recent anti-lymphoma therapy status
Refractory 103 52 (42-62)
Relapse 52 83 (70-92)
Positive bone marrow involvement by biopsy/ aspiration
Yes 58 50 (37-63)
No 88 73 (62-82)
Ann Arbor staging
III/IV 136 61 (52-69)
Baseline FLIPI
2 31 71 (52-86)
3-5 78 53 (41-64)
0
20
40
60
80
100
Complete Response Rate(%)


Subgroups
No. of Patients
Complete Response Rate % of Patients (95% CI)
Overall presence of ADAs
Non-Positive 144 63 (55-71)
Bulky disease by IRC at baseline
Nodal or extranodal mass >6 cm 38 66 (49-80)
Nodal or extranodal mass <=6 cm 117 62 (52-70)
Nodal or extranodal mass <=7 cm 136 63 (55-71)
Progression, transformation, or relapse within 24 months of initiating first line immunochemotherapy
Yes 63 59 (46-71)
No 92 65 (55-75)
Progression, transformation, or relapse within 24 months from any first line therapy
Yes 78 62 (50-72)
No 77 64 (52-74)
0
20
40
60
80
100
Complete Response Rate(%)



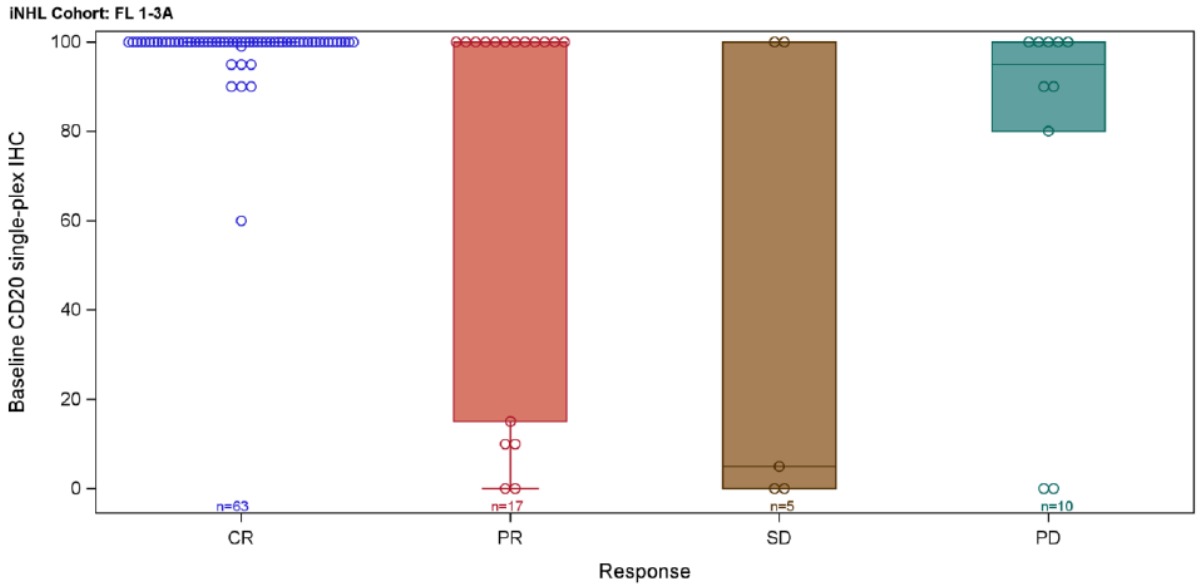
Note: Subgroups with fewer patients (N < 20) are excluded.

CD20 expression levels

All subjects enrolled in the study, as required per eligibility criteria, were CD20 positive based on a previously assessed representative biopsy (at baseline or earlier).

Tumor biopsy samples submitted at screening were also assessed for CD20 expression by IHC at a central laboratory (CellCarta) in 97 subjects with FL. CD20 expression was assessed by BOR category based on IRC assessment determined by Lugano criteria. CD20 expression was reported as % tumor cells positive for CD20 staining.

Figure 16: Summary of Baseline CD20 Expression by Response Group - GCT3013-01 Expansion Part - Subjects in iNHL Cohort – Full Analysis Set



Note: Y axis is the percentage of CD20 positive tumor cells.
Response categories are based on IRC assessment per Lugano criteria.

Data show that of the FL patients enrolled in the iNHL expansion cohort of Study GCT3013-01, seven patients were CD20 negative according to local assessment. Of these CD20 negative patients, 2 had notable observed treatment response (CR or PR).

Further, among the 10 subjects who were response evaluable and showed low CD20 expression by central assessment, 5 subjects were responders (PR) and 5 subjects were non-responders (SD, PD).

Duration of Complete Response Determined by Lugano Criteria

The median DOCR for subjects with FL based on IRC assessment was NR (95% CI: 21.4, NR). The median DOCR follow-up was 13.4 months (range: 0.0+, 26.3+). The estimated percentage of subjects with FL remaining in response at 12 and 18 months was 82.2% and 72.2%, respectively.

Similar results for DOCR based on IRC assessment (Lugano criteria, primary definition) were observed in RES.

Among subjects with FL, the DOCR of most subgroups, including those with high-risk disease characteristics, were similar to that observed in the overall population.

The median DOCR based on investigator assessment was NR (95% CI: NR, NR), in subjects with FL, with a median follow-up for DOCR of 14.6 months (range: 0.0+, 26.3+). The estimated percentage of subjects with FL remaining in response at 12 and 18 months was 77.5% and 67.4%, respectively.

Sensitivity analysis ORR

As a sensitivity analysis, ORR results evaluated by the independent radiologists using only MRI/CT-based Lugano criteria for response was conducted. Using this methodology, ORR for the subjects with FL was 73.4% (95% CI: 64.9, 80.9). Similar results for CT-based ORR were observed for subjects with FL in RES population.

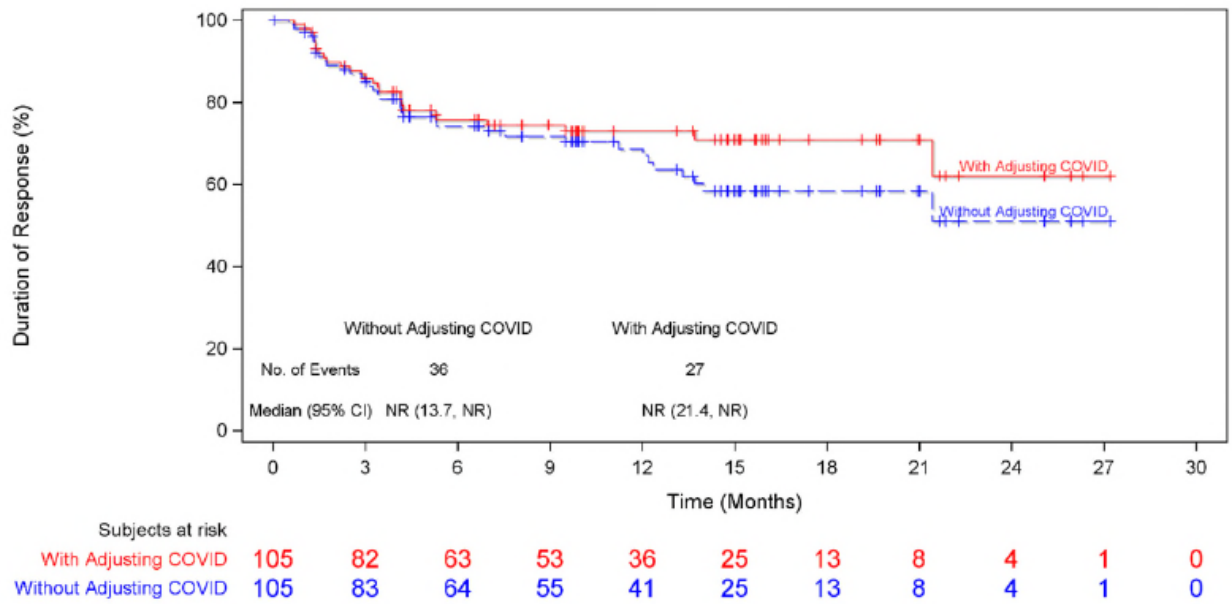
ORR for the subjects with FL in mFAS was 73.0% (95% CI: 63.2, 81.4).

Impact COVID-19 pandemic

The FL Expansion Part of the GCT3013-01 trial was conducted entirely during the coronavirus disease 2019 (COVID-19) pandemic, and at a time when the highly infectious Omicron variants were prevalent globally. The first subject signed informed consent on 19 June 2020 and the clinical DCO was 21 April 2023.

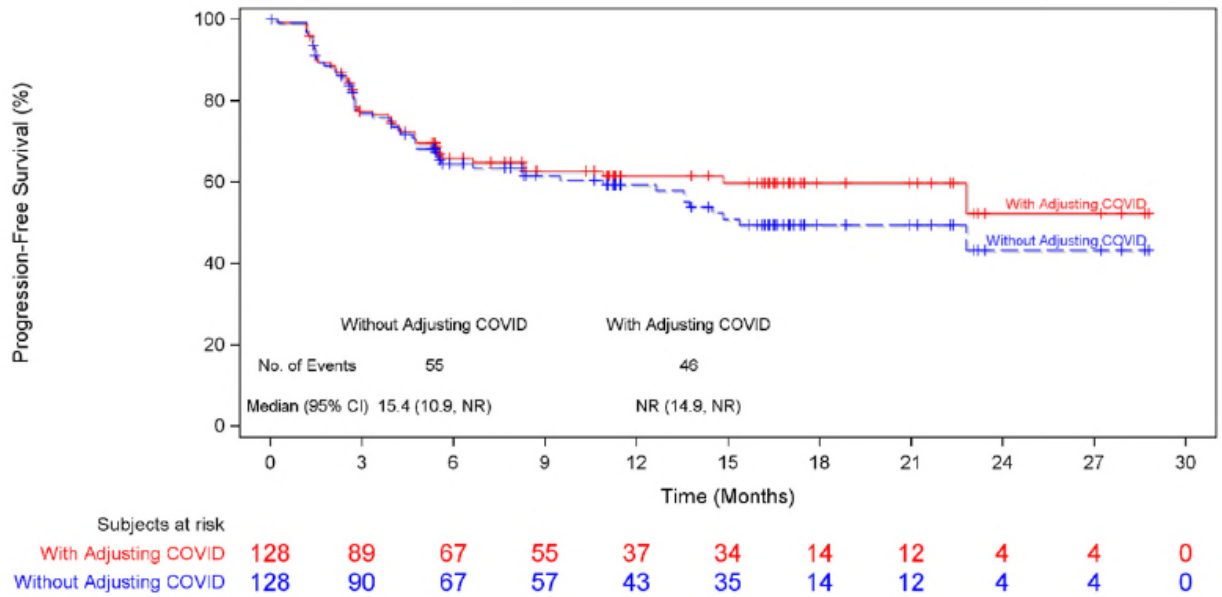
Sensitivity analyses were performed to evaluate whether COVID-19 associated deaths may have impacted (i.e., shortened) the observed DOR, PFS, or OS in subjects with FL in the iNHL Expansion Part of Study GCT3013-01. Based on a median follow-up of 14.8 months, the median DOR among subjects with FL was NR (95% CI: 21.4 months, NR) when adjusted for COVID-19 deaths. The estimated percentage of subjects remaining in response at 12 and 18 months was 73.1% and 71%, respectively, when adjusted for COVID-19 deaths, compared with 68.7% and 58.4%, respectively, without adjustment (Figure 19). Similar impacts due to COVID-19 deaths in responding subjects were observed on PFS and OS (Figure 20, Figure 21).

Figure 17: Kaplan-Meier Plot of Impact of COVID-19 Associated Deaths on DOR, Based on IRC Assessment, Lugano Criteria



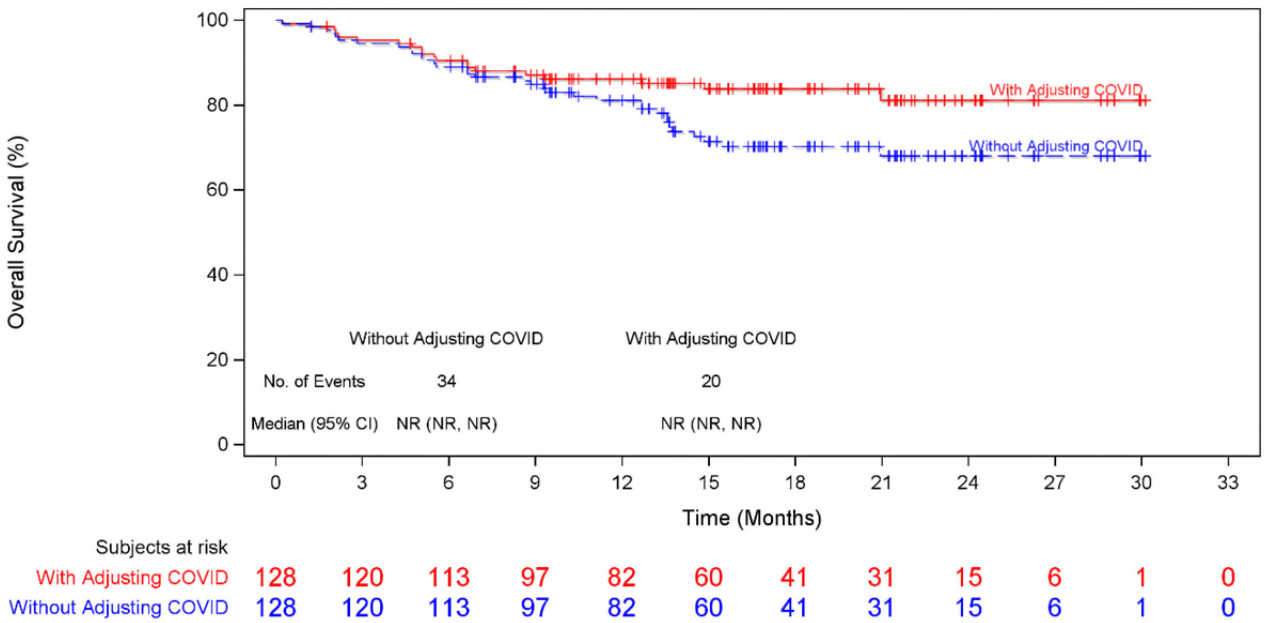
CI = confidence interval; COVID-19 = coronavirus disease 2019; DCO = data cutoff; DOR = duration of response; IRC = independent review committee; No. = number; NR = not reached.

Figure 18: Kaplan-Meier Plot of Impact of COVID-19 Associated Deaths on PFS, Based on IRC Assessment, Lugano Criteria



CI = confidence interval; COVID-19 = coronavirus disease 2019; DCO = data cutoff; IRC = independent review committee; No. = number; NR = not reached; PFS = progression-free survival.

Figure 19: Kaplan-Meier Plot of Impact of COVID-19 Associated Deaths, on OS



Upon CHMP request, the MAH also provided additional sensitivity analyses for DOR:

- A sensitivity analysis where new anti-lymphoma therapy administration is considered as an event and time to administration is considered as event time, was conducted. For this sensitivity analysis the median DOR (as assessed by the IRC using Lugano criteria) for subjects with FL in the iNHL

expansion cohort was 20.7 months (95% CI: 12.2, NR).

- After 24 weeks the time between assessments is increased to 12 weeks and after 48 weeks to 24 weeks. Two sensitivity analyses in which the progression time is assigned (i) at the midpoint, and (ii) at the lower limit of the censoring interval (i.e., shortly after the previous assessment) were performed and consistent with the primary analysis.

Further, the impact of the selection adaptive element (i.e., interim decision to continue the study) on the estimation of the ORR and DoR was analysed. In line with expected bias in an interim analysis to decide to proceed if interim results are positive, the ORR was numerically more optimistic in the stage interim analysis (87.9%) than in the stage 2 (80.8%), but the updated overall ORR (82.8%) was close to the stage 2 result. This was also reflected in CR (interim: 69.7%; update: 63.3%; stage 2: 61.5%). Median DoR was similar (interim: 23.6 months; update: 23.6).

Summary of main study

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 19: Summary of Efficacy for trial

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	
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 a Dose Escalation Part, an Expansion Part and an Optimization Part. The expansion part is considered to be the pivotal study by the MAH. The Expansion Part consists of 3 cohorts enrolling aggressive B-cell non- The Expansion Part of the trial was initiated with parallel enrollment in 3 cohorts of subjects with distinct B-cell lymphoma subtypes: R/R aNHL cohort (LBCL), R/R iNHL cohort (including FL Grade 1-3A), and R/R MCL cohort who were treated with the RP2D of epcoritamab. The iNHL cohort is the pivotal cohort for this submission.	
	Duration of main phase:	First subject first visit for the expansion part of the trial was 19 June 2020
	Duration of Run-in phase:	The study is currently ongoing; clinical cut-off date 21 April 2023
	Duration of Extension phase:	Not applicable
Hypothesis	No formal statistical hypotheses were formulated in this trial.	

Treatments groups	Expansion part. iNHL Cohort: iNHL patients including (FL grade 1-3A)who were previously treated with at least 2 lines of systemic antineoplastic therapy including at least 1 anti-CD20 monoclonal antibody-containing therapy		iNHL cohort 155 patients received at least 1 dose of epcoritamab, including 128 patients diagnosed with FL Grade 1-3A and 27 patients with other iNHL subtypes (i.e. MZL and SLL). <u>Treatment</u> 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	ORR	determined by Lugano criteria as assessed by independent review committee (IRC)
	Key secondary endpoints	DOR	
		CR rate	
		PFS	
		OS	defined as the time from Day 1 of Cycle 1 to death
		TTNT	defined as the time from Day 1 of Cycle 1 to first recorded administration of subsequent anti-lymphoma therapy or death due to any cause
		MRD negativity	defined as the proportion of patients with at least one MRD- sample
Database lock	21 April 2023		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	**Full Analysis Set (FAS):** All enrolled subjects who have been exposed to at least one dose of epcoritamab.		
Descriptive statistics and estimate variability	Treatment group	FAS	FL 1-3A
	Number of subject	155	128
	ORR (PR or CR by IRC) n (%)	128 (82.6%)	105 (82.0%) Updated ORR per DCO 16 Oct 2023 in FL1-3A 82.8% (106)

	Median DOR (by IRC)	21.4 (95% CI 14.0, NR after median follow up of 14.2 (95 CI 9.9, 14.9) months	NR (95% CI 13.7, NR) after median follow up of 14.8 (95% CI 10.0, 15.2) months Updated DOR per DCO 16 Oct 2023 in FL1-3A 23.6 (13.8, NR)
	Estimated percentage of subjects remaining in response at 12 and 18 months (95% CI)	70.3% (60.6%, 78.1%) 55.0% (42.6%, 65.8%)	68.7% (58.0%, 77.3%) Updated per DCO 16 Oct 2023 in FL1-3A 62.3% (52.2%, 70.9%) 58.4% (46.4%, 68.7%) Updated per DCO 16 Oct 2023 in FL1-3A 53.7% (43.2%, 63.1%)
	CR (by IRC), n (%)	97 (62.6%)	80 (62.5%) Updated CR per DCO 16 Oct 2023 in FL1-3A 63.3% (81)
	PFS (by IRC)	16.0 (95% CI 13.6, NR) after median follow-up of 15.7 months (95% CI 11.3, 16.5)	15.4 (95% CI 10.9, NR) after median follow-up of 16.1 (95% CI 11.3, 16.8) Updated PFS per DCO 16 Oct 2023 in FL1-3A15.4 (95% CI 10.9, NR) after median follow-up of 17.5 (95% CI 16.6, 21.9)
	Estimate percentage of patients remaining progressive free at 15 months and 21 months (95% CI)	52.5% (42.8%, 61.2%) 46.5% (35.4%, 56.9%)	50.9% (40.5%, 60.4%) Updated per DCO 16 Oct 2023 in FL1-3A 52.1% (42.3%, 60.9%) 49.4% (39.1%, 59.1%) Updated per DCO 16 Oct 2023 in FL1-3A 49.8% (40.0%, 58.8%)

	OS	NR (95% CI NR, NR) after median follow up of 17.0 months (95% CI 15.7, 18.7)	NR (95% CI NR, NR) after median follow up of 17.4 months (95% CI 15.8, 19.8) Updated OS per DCO 16 Oct 2023 in FL1-3A NR (95% NR, NR) after a follow up of 22.9 (95% CI 20.6, 24.2)
	Estimate percentage of patients remaining alive at 15 months and 21 months (95% CI)	73.2% (64.4%, 80.1%) 67.4% (57.3%, 75.6%)	71.4% (61.8%, 79.0%) Updated per DCO 16 Oct 2023 in FL1-3A 74.2% (65.5%, 81.0%) 68.0% (57.5%, 76.4%) Updated per DCO 16 Oct 2023 in FL1-3A 69.9% (60.6%, 77.4%)
	TTNT	NR (95% CI NR, NR) after median follow up of 15.7 months (95% CI 13.7, 17.0)	NR (95% CI NR, NR) after median follow up of 16.4 months (95% CI 14.5, 17.5) Updated TTNT per DCO 16 Oct 2023 in FL1-3A NR (95% 26.5, NR) after a follow-up of 21.0 (95% CI 19.1, 23.0)
	Estimate percentage of patients not initiating next line of therapy at 15 months and 21 months (95% CI)	67.0% (58.4%, 74.2%) 65.2% (56.0%, 72.9%)	63.3% (53.7%, 71.4% Updated per DCO 16 Oct 2023 in FL1-3A 63.6 % (54.3%, 71.5%) 61.1% (50.9%, 69.8%) Updated per DCO 16 Oct 2023 in FL1-3A 61.1 % (51.6%, 69.4%)
	MRD negativity		67.0% (95% CI 56.4%, 76.5%)
Effect estimate per comparison	Not applicable, single-arm study		

Analysis performed across trials

Indirect treatment comparisons of epcoritamab vs. comparators in r/r FL after two or more systemic therapies

A comparative analysis of epcoritamab versus key currently available therapies (i.e., comparators) in relapsed or refractory follicular lymphoma subjects after at least two systemic therapies, was conducted.

Given that GCT3013-01 and comparator trials (chemo-immunotherapy [CIT] (SCHOLAR-5), mosunetuzumab (GO29781, NCT02500407), tisagenlecleucel [tisa-cel] (ELARA, NCT03568461), and axicabtagene ciloleucel [axi-cel] (ZUMA-5, NCT03105336)) were uncontrolled trials, indirect treatment comparisons (ITCs) were conducted using the matching adjusted indirect comparisons (MAIC)

approach, with individual patient data from the FL (grade 1-3A) cohort of GCT3013-01 iNHL arm and published aggregate data of the relevant comparators. The used MAICs approach was proposed by Signorovitch et al. (2012) and Lee et al. (2011) and implemented in R (R Foundation for Statistical Computing, 2015), propensity score weights were applied to the overlapping patient populations in GCT3013-01 and comparator trials to create balanced distributions of key baseline characteristics this cohort with each of the comparator trials, in terms of measured effect modifiers and prognostic factors. The selection of key baseline patient characteristics used for matching was determined based on literature review and clinical input.

Notable differences in the inclusion/ exclusion criteria of these trials were identified based on publicly available information on the trial protocols of comparators. Overall, GCT3013-01 enrolled a higher proportion of older subjects, later lines of therapy, double refractory disease (i.e., refractory to an anti-CD20 containing regimen and an alkylator), and FLIPI ≥3, compared to respective competitor trials for mosunetuzumab, tisa-cel, and axi-cel. Further, the trials enrolled, and followed subjects (i.e., collected data) at different times.

For the overlapping patient populations represented in the epcoritamab trial and comparator trials, indirect treatment comparisons (ITCs) of the response rates for epcoritamab vs. CIT, mosunetuzumab, tisa-cel, and axi-cel were conducted. Response rates were compared for these therapies before and after adjusting/ weighting and matching trial cohorts based on the distribution of key demographic and clinical variables such as age, sex, ECOG performance status, disease stage, FLIPI, number of prior lines of therapy, prior stem cell transplantation, POD24, double refractory disease, refractory to last line of therapy, LDH, depending on the data reported by the comparator studies.

Results

Table 20: Summary of key patient characteristics and outcomes of GCT3013-01 and comparator trials in R/R FL

	GCT3013-01 trial	GO29781 Budde et al. 2022	ELARA Fowler et al. (2022)	ZUMA-5 Jacobson et al. 2022		SCHOLAR-5 Ghione et al.(2023)[a]
Therapy	**epcoritamab**	**mosunetuzumab**	**tisa-cel**	**axi-cel**		**CIT**
Total N	128	90	97	124		205[a]
Trial design	Open label, ph.1/2	Open label, ph.2	Open label, ph.2	Open label, ph. 2		Observational, RWE
Comparator in trial	No comparator	No comparator	No comparator	No comparator		No comparator
Median age, years	65.0	60	57	60		
Age ≥65 years, %	67 (52.3%)	30 (33.3%)	24 (24.7%)	38 (31%)		53.5%[a]
Male, %	79 (61.7%)	55 (61%)	64 (66.0%)	73 (59%)		58.4%[a]
ECOG 0-1, %	121 (94.5%)	90 (100%)	100%	100%		-
Median N of prior LOTs (range)	3 (2 to 9)	3 (IQR 2 to 4)	4 (2 to 13)	3 (IQR 2 to 4)		-
Double refractory, %	90 (70.3%)	48 (53%)	66 (68.0%)	74 (58.3%)		-
FLIPI ≥3	78 (60.9%)	40 (44%)	58 (59.8%)	54 (44%)		35.4%[a]
Ann Arbor Stage III/IV	109 (85.2%)	69 (76.7%)	83 (85.6%)	106 (85%)		85.4%[a]
≥3 prior LOT, %	81 (63.3%)	56 (62%)	-	78 (63%)		57.6%[a]
Prior ASCT, %	24 (18.8%)	19 (21%)	35 (36.1%)	30 (24%)		20.0%[a]
Prior CAR T, %	6 (4.7%)	3 (3%)	0%	0 (0%)		0%[a]
Response rates reported from the respective trials[b]						
ORR	82.0%	80%	86.2%	94%		56.8%[a]
CR	62.5%	60%	69.1%	79%		32%[a]

[a]SCHOLAR-5 reported outcomes by mutually exclusive lines of therapy (LOT). From an N of 128, there were 205 eligible LOTs. Double refractory = refractory disease to an anti-CD20 containing regimen and an alkylating agent. The % for SCHOLAR-5 are reported without the patients with missing values (i.e., prior SCT had 1 missing; disease stage had 28 missing, ECOG had 27 missing), FLIPI had 40 missing. SCHOLAR-5 response rates are based on investigator assessment and the distribution of baseline characteristics and pooled ORR/CR are derived/ estimated based on a weighted aggregation of ORR/CR by individual LOTs as reported in Ghione et al. 2023.
[b]ORR and CRs reported in the various trials were based on evaluable patients and that number was different than the total N at the top of the table in some cases

Epcoritamab vs. CIT

Since SCHOLAR-5 outcomes were reported by mutually exclusive LOTs (3L, 4L, and 5L), weighted and pooled estimates of ORR and CR were generated for 3L. The GCT3013-01 cohort was adjusted to match the SCHOLAR-5 cohort a with estimated distributions of key variables before and after adjustment. After adjusting the GCT3013-01 population to the SCHOLAR-5 population, the baseline characteristics were balanced between the two comparators, including age ≥ 65 years, sex, ECOG status, disease stage III-IV, FLIPI 3, prior CAR-T, prior ASCT, POD24, refractoriness to last prior therapy, 3 prior LOTs, and the proportion of patient with bulky disease.

Table 21: Unadjusted and adjusted response rates for epcoritamab vs. CIT

	epcoritamab (GCT3013-01) (N = 128)[h]	CIT (SCHOLAR-5) (n=205)[j]	Odds ratios [95%CI], p-value
Unadjusted response rates			
ORR (%)	82.0	56.8	3.473 [2.041, 5.909], p<0.001
CR (%)	62.5	32.0	3.535 [2.221, 5.626], p<0.001
Adjusted response rates			
ORR (%)	**90.9**	**56.8**	**7.583** [3.341, 17.212], p<0.001
CR (%)	**73.7**	**32.0**	**5.951** [3.069, 11.542], p<0.001

ORR = overall response rates; CR = complete response rates; CI = confidence interval
[h]The adjusted response rates are based on an effective sample size of 44
[j]N of ~205 is from all eligible LOTs from 128 subjects in SCHOLAR-5

Epcoritamab vs. mosunetuzumab

Among the 128 GCT3013-01 subjects with FL, 81 subjects were overlapping with the GO29781 population, and these were included in the MAIC of epcoritamab vs. mosunetuzumab. After adjusting the GCT301-01 and the GO29781 populations were balanced for the key variables, including age ≥60 years, sex, ECOG status, proportion of disease stage III-IV, proportion of FLIPI 3, prior CAR-T, prior ASCT, POD24, proportion of refractory to last prior therapy, proportion of refractory to any previous anti-CD20 therapy, double refractory, proportion of refractory to last prior therapy, proportion of subjects with >3 prior LOTs, and proportion of subjects with bulky disease (>6cm in diameter) without balancing the cohorts based on prior R2 exposure.

Table 22: Unadjusted and adjusted response rates for epcoritamab vs. mosunetuzumab

	epcoritamab (GCT3013-01, N = 81)[m]	mosunetuzumab (GO29781, N=90)	Odds ratios [95%CI], p-value
Unadjusted response rates			
ORR (%)	84.0	80.0	1.308 [0.591, 2.895], p=0.506
CR (%)	67.9	60.0	1.41 [0.747, 2.662], p=0.287
Adjusted response rates			
ORR (%)	**84.3**	**80.0**	**1.345** [0.521, 3.468], p=0.538
CR (%)	**69.9**	**60.0**	**1.546** [0.735, 3.249], p=0.249

ORR = overall response rates; CR = complete response rates; CI = confidence interval
[m]The adjusted response rates are based on an effective sample size of 47

Epcoritamab vs. tisa-cel

Ninety (90) out of the 128 GCT3013-01 subjects with FL were overlapping with the ELARA trial population based on inclusion criteria, and these 90 subjects were included in the MAIC of epcoritamab vs. tisa-cel. After adjusting the 90 GCT3013-01 subjects to match the ELARA trial population on the distribution of key variables, the baseline characteristics were balanced between the two comparators, including age, sex, ECOG status, disease stage (III-IV), FLIPI 3, prior ASCT, POD24, refractoriness to any previous anti-CD20 therapy, double refractory disease, refractoriness to last prior therapy, elevated LDH, and >4 prior LOTs. No matching was conducted based on bulky disease due to differences in the definitions applied across the trials.

Table 23: Unadjusted and adjusted response rates for epcoritamab vs. tisa-cel

	epcoritamab (GCT3013-01) (N = 90)[P]	tisa-cel (ELARA, N=97)	Odds ratios [95%CI], p-value
Unadjusted response rates			
ORR (%)	86.7	86.2	1.043 [0.445, 2.445], p=0.922
CR (%)	66.7	69.1	0.938 [0.503, 1.747], p=0.838
Adjusted response rates			
ORR (%)	**85.5**	**86.2**	**0.948** [0.321, 2.802], p=0.923
CR (%)	**65.7**	**69.1**	**0.900** [0.419, 1.933], p=0.785

ORR = overall response rates; CR = complete response rates; CI = confidence interval
[P]The adjusted response rates are based on an effective sample size of 44

Epcoritamab vs. axi-cel

Ninety-one (91) out of the 128 GCT3013-01 subjects with FL were overlapping with ZUMA-5 based on inclusion criteria, and these 91 were included in the MAIC of epcoritamab vs. axi-cel. After adjusting the 91 GCT3013-01 subjects to match the ZUMA-5 trial population on the distribution of key variables,

the baseline characteristics were balanced between the two groups, including age, sex, ECOG status, disease stage (III-IV), FLIPI 3, prior ASCT, POD24, refractoriness to last prior therapy, and 3 prior LOT. Due to differences in the definition of bulky disease across the trials, there was no matching based on this variable.

Table 24: Unadjusted and adjusted response rates for epcoritamab vs. axi-cel

	Epcoritamab (GCT3013-01) (N = 91)[w]	Axi-cel (ZUMA-5, N = 124)	Odds ratios [95%CI], p-value
Unadjusted response rates			
ORR (%)	83.5	93.7	0.341 [0.137, 0.848], p=0.021
CR (%)	63.7	78.7	0.475 [0.258, 0.871], p=0.016
Adjusted response rates			
ORR (%)	**86.2**	**93.7**	**0.419** [0.159, 1.105], p=0.078
CR (%)	**65.5**	**78.7**	**0.513** [0.271, 0.972], p=0.041

ORR = overall response rates; CR = complete response rates; CI = confidence interval
[w]The adjusted response rates are based on an effective sample size of 76

Supportive study(ies)

FL GCT3013-01, Optimization Cohort

The aim of the FL optimization cohort was to investigate different SUD regimens in order to reduce the rate of ≥ grade 2 CRS events and all grade CRS events from the first dose of epcoritamab through 7 days following administration of the second full dose of epcoritamab.

Subjects in the Dose Expansion Part of this trial received the 2-step SUD 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). The FL optimization cohort investigated 2 alternative 3-step SUD regimens along with adequate hydration and dexamethasone premedication in Cycle 1 in subjects with FL grades 1-3A to reduce the risk of ≥ grade 2 CRS and all grade CRS. The 2 alternative dosing regimens administered to subjects in the FL optimization cohort included a second intermediate dose (Arm A: 3 mg; Arm B: 6 mg) administered on C1D15 followed by a full dose on C1D22 and thereafter (Table *51*). Reference is made to the safety section for a more detailed description of the methods and results for the optimization cohort.

The primary objectives of the optimization phase concerned safety, however some efficacy data was collected. Preliminary safety, efficacy, PK, and PD data from an unplanned analysis have been provided.

At the cutoff date of 31 Jun 2023, 30 patients were enrolled in Arm A and 6 patients were enrolled in Arm B. All patients have been exposed to at least one dose of epcoritamab (Full Analysis Set). Baseline characteristics are generally comparable to those of subjects with FL enrolled in the iNHL expansion cohort of the GCT3013-01 trial. The median duration of trial follow-up for patients included in Arm A, was 3.9 months (range; 1.9, 8.7). All efficacy evaluation were assessed by the investigator according to Lugano criteria.

The ORR in subjects in Arm A was 83.3% (95% CI: 65.3%, 94.4%), CR rate was 56.7% (95% CI: 37.4%, 74.5%) and PR rate was 26.7%.

The median TTR was 1.4 months (range: 1.2, 4.4) and the median TTCR was 1.4 months (range: 1.3, 4.2).

Updated data

The ORR based on investigator assessment by Lugano criteria in subjects in Arm A of the FL optimization cohort as of the DCO of 08 January 2024 was 86.0% (95% CI: 76.9, 92.6), and the CR rate was 64.0% (95% CI: 52.9, 74.0).

Among the subjects in Arm A of the FL optimization cohort who achieved PR or CR (n = 74), the median DOR follow-up was 2.8 months. The median DOR based on investigator assessment per primary definition was NR (95% CI: NR, NR).

DOR results per secondary definition were consistent with those of the primary definition.

FL cohort of the Monotherapy Expansion part of the GCT3013-04 study

Study GCT3013-04 is a phase 1/2, open-label, single-country, interventional trial in Japanese subjects with r/r B-NHL. The trial included 2 parts; a dose escalation part and an expansion part. It was planned to include approximately 20 subjects in the FL Grade 1-3A cohort. Epcoritamab was administered (SC) in treatment cycles of 4 weeks (i.e., 28 days) 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 PD, unacceptable toxicity, or end of trial: Day 1 (Q4W)

A priming dose of 0.16 mg was administered on C1D1, followed by an intermediate dose of 0.8 mg on C1D8 and a full dose of 48 mg on C1D15 and thereafter.

CRS prophylaxis with corticosteroids and premedication with antihistamines and antipyretics was mandatory.

The primary endpoint of ORR was defined as the proportion of subjects who achieved a BOR of CR or PR in an analysis set. ORR was evaluated by the investigator and was also evaluated by the IRC. The primary analysis was planned to be conducted approximately 6 months after the last subject's first dose for the Monotherapy Expansion Part.

Secondary endpoints were IRC-assessed OR per Lyric, DOR, CR rate, DOCR, PFS, TTR, TTCR, OS, TTNT, and rate of MRD negativity.

As the date cutoff date of 21 April 2023, a total of 21 subjects were enrolled in the FL expansion cohort across 12 sites in Japan.

All 21 subjects enrolled received at least 1 dose of epcoritamab and were, therefore, included in the FAS/Safety Analysis Set. As of the cutoff date of 21 April 2023, 15 (71.4%) subjects discontinued epcoritamab treatment due to progressive disease (7 subjects), AEs (4 subjects), subjects requested to discontinue trial treatment (2 subjects), and for 'other' reasons (2 subjects). For the 2 subjects who discontinued epcoritamab for 'other' reasons, 1 subject discontinued due to risk of COVID-19 recurrence and 1 subject discontinued due to investigator decision. Six (28.6%) subjects continue to receive epcoritamab treatment. Two (9.5%) subjects permanently discontinued the trial; trial discontinuation was due to death and subject withdrawing consent from the trial (1 [4.8%] subjects each).

All subjects were of Asian race and Japanese ethnicity, as required per protocol. A total of11 (52.4%) subjects were male. The median age was 65.0 years (range: 58, 75), including 2 (9.5%) subjects who

were ≥ 75 years of age. Most subjects (95.2%) had a baseline ECOG performance status of 0 (a status of 0, 1, or 2 was required for inclusion).

All subjects had a diagnosis of FL Grade 1-3A.The median time from initial diagnosis was 8.397 years. Eight (38.1%) subjects had FL Grade 3A disease; 17 (81.0%) of the subjects had advanced staged lymphoma (Ann Arbor Stage III and IV disease), with 10 [47.6%] subjects had Ann Arbor Stage IV disease; 11 (52.4%) subjects had a FLIPI score ≥ 3. Baseline bone marrow involvement as assessed by the investigator was present in 4 (19.0%) subjects. Twelve (57.1%) subjects were double refractory to anti-CD20 and alkylating agent and 12 (57.1%) subjects had POD24 from any first line therapy. The median time from last anti-lymphoma therapy to first dose was 10.84 months

Subjects received a median of 4.0 lines of prior anti-lymphoma therapies (range: 2, 10). All subjects received at least 2 prior systemic lines of anti-lymphoma therapy, including an anti-CD20 mAb containing therapy and alkylating agents, as required per protocol, 16 (76.2%) subjects received anthracyclines, and 5 (23.8%) received lenalidomide. Four (19.0%) subjects had a prior ASCT, with 1 (4.8%) subject relapsing within 12 months after ASCT. No subjects had received prior CAR-T cell therapy. Additionally, 17 subjects received prior bendamustine treatment. A total of 10 (47.6%) subjects were refractory to the last line of systemic antineoplastic therapy and 7 (33.3%) subjects were refractory to > 2 consecutive lines of prior therapy. The population of FL subjects was overall heavily pre-treated, and highly refractory.

A total of 6 (28.6%) subjects received a subsequent anti-lymphoma therapy, including 2 (9.5%) subjects who received CAR T-cell therapy. No subjects received subsequent radiotherapy, new tumour directed surgery, or stem cell transplant. The most common subsequent systemic therapies received were bendamustine, cyclophosphamide, etoposide, rituximab, and zandelisib.

Efficacy results

As of the data cutoff date of 21 April 2023, the median duration of follow-up was 21.2 months (range: 18.0, 24.0) for the FL expansion cohort.

The ORR (CR + PR) for subjects in the FL expansion cohort was 95.2% (95% CI: 76.2%, 99.9%), with 76.2% (16 subjects) and 19.0% (4 subjects) in subjects achieving best response of CR and PR, respectively.

After a median DOR follow-up of 15.3 months (95% CI: 9.7, 20.6), the median DOR (Lugano criteria, primary definition) was 23.1 months (95% CI: 4.4, NR) for subjects who achieved PR or CR (n=20). The estimated percentage of subjects remaining in response at 12 and 18 months was 68.4% and 60.8%, respectively. The median DOCR was 23.1 months (95% CI: 15.0, NR). The estimated percentage of subjects who achieved CR remaining in complete response at 12 and 18 months was 81.3% and 71.1%, respectively.

For the 16 subjects who achieved CR, the median TTCR was 1.4 months (range: 1.2, 2.8).

A total of 8 (38.1%) subjects experienced a PFS event (disease progression or death) per the primary definition based on IRC assessment determined by Lugano criteria. After a median PFS follow-up of 16.7 months (95% CI: 10.9, 21.9), the median PFS was 24.3 months (95% CI: 5.7, NR). The estimated percentage of subjects remaining in response at 21 and 24 months was 61.4%. Analysis of PFS by BOR showed that subjects who achieved a PR had a median PFS of 2.6 months (95% CI: 2.5, NR), whereas subjects who achieved a CR had a median PFS of 24.3 months (95% CI: 16.4, NR).

At the time of data cutoff, there was 1 (4.8%) subject who died, and 20 (95.2%) subjects who were still alive. After a median OS follow-up of 21.2 months (95% CI: 18.0, 24.0), the median OS was not

reached (95% CI: 24.3, NR). The estimated percentage of subjects who remained alive at 21 and 24 months was 100% for each.

A total of 6 (28.6%) subjects experienced a TTNT event, and 15 (71.4%) subjects were censored. After a median follow-up of 20.1 months, the median TTNT was not reached. The estimated percentage of subjects not initiating subsequent therapy at 18, 21, and 24 months was 71.4% for each.

Using the PBMC assay with a 10-6 cutoff, 16 of 18 (88.9% [95% CI: 65.3%, 98.6%]) MRD-evaluable subjects were assessed as MRD negative. Subjects with FL who achieved MRD negativity had improved PFS compared to subjects who were MRD-positive.

Real Word data; Real-World Treatment Patterns and Clinical Outcomes for Follicular Lymphoma in COTA Electronic Medical Records

This retrospective cohort study included patients with both a recorded diagnosis of FL and third-line and later treatment at any time from January 2010 through December 2022 using longitudinal data from the COTA electronic health records (EHR database (COTA, New York, NY, USA). The COTA EHR database houses de-identified demographic and clinical information, including diagnostic, treatment, and outcomes data, from US community practice sites and academic medical centers for an estimated 4225 adult patients with FL.

For inclusion in the study, patients had histologically confirmed grade 1, 2, or 3A FL at initial diagnosis without clinical or pathologic evidence of transformation. Initiation of their third line therapy must have been on or after January 1, 2010. Patients also had R/R disease previously treated with ≥2 systemic antineoplastic therapies, including ≥1 anti-CD20 mAb– containing regimen and ≥1 regimen with an alkylating agent or lenalidomide. Relapsed disease was defined as disease that recurred ≥6 months after completion of the last therapy. Being refractory to anti-CD20 mAb or alkylating therapy was defined as the initiation of a new therapy or noted PD within 6 months of ending a prior regimen containing anti-CD20 mAb or alkylating therapy. Patients also had been treated with a usual care regimen in the third-line or later therapy setting, and were ≥18 years of age at initiation of third-line therapy. Finally, patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status ≤2 at 3L initiation, ≥3 months of follow-up after third-line initiation, and ≥1 evaluable response assessment or a date of death after third-line initiation, if the death occurred before the post-third-line–initiation evaluable response assessment. Therapies were excluded if comprised of an investigational agent at or after third-line initiation, as this analysis aimed to capture usual care treatment.

The index date for a given included subjects was defined as the initiation date of the first treatment. The pre-index baseline period was defined as the time between the first confirmed FL diagnosis and the index date (inclusive). The observation period was defined as the duration from third-line initiation until end of follow-up, defined as death, last activity date, or last date of data collection, whichever occurred first.

Efficacy outcomes included ORR, complete response (CR) rate, duration of response (DOR), and time to next treatment or death (TTNT-D), progression-free survival (PFS), and OS. ORR was defined as the proportion of patients with CR or partial response (PR) of any duration as the best documented response for the relevant therapy, as retrieved from clinician documentation in Electronic health records (EHR). Response was clinician determined. Imaging scans utilization and results were not available in the COTA database. CR was defined as the proportion of patients with CR of any duration as the best documented response for the relevant line of therapy. DOR was defined as the time from the first documentation of CR or PR to the earliest of first documented PD or all cause death. DOR was only calculated for patients who achieved CR or PR for the relevant therapy. TTNT-D was defined as

the time from the relevant therapy initiation date to the subsequent therapy initiation date for patients with a subsequent therapy or time to death for patients who died prior to subsequent therapy initiation. PFS was defined as the time from initiation of the relevant therapy to the earliest of first documented PD or all-cause death. OS was defined as the time from initiation of the relevant therapy to all-cause death.

Continuous variables are presented as mean (standard deviation [SD]) and median (range) values, and categorical variables as frequencies and percentages. For response outcomes (ORR, CR, and PR), the total number and proportion of patients (including 95% CI) are reported. Time-to-event parameters (DOR, TTNT-D, PFS, OS) and the proportion of patients with these outcomes at 6, 12, and 24 months are described using Kaplan-Meier estimates (median time with corresponding 95% CIs and frequencies with percentages). For DOR and PFS, patients without an assessment of PD or death before initiating the subsequent therapy were censored at the date of their last clinical assessment. For TTNT patients without record of initiating a subsequent therapy were censored at the date of death or last follow-up. For OS, patients with no death date were censored at the date of last recorded follow-up. Log-rank tests were used to determine the significance between prognostic factors and OS, with statistical significance set at $P<0.05$.

Results

In total, 240 patients with FL who had been treated with third-line or later line of therapy contributed 376 eligible therapies for inclusion in this analysis. Of these eligible therapies, 218 were administered as third-line, 91 as fourth-line, and 67 as fifth-line or later. At the time of line initiation, mean (SD) patient age was 67.1 (11.0) years and median (range) patient age was 67.7 (35.1–91.8) years. Over half (56.6%) were male and most were White (91.0%). Median (range) duration of follow-up from initiation of third-line treatment was 50.0 (3.0–147.0) months. The median (range) number of prior lines of therapy was 2.0 (2.0–8.0). A total of 2.9% of patients had prior CAR T, 5.3% had prior autologous stem cell transplant, and 33.5% had FL that was primary refractory. With respect to prognostic features, 25.3% had FLIPI scores ≥3, 50.8% had double-refractory disease, 80.1% received treatment at community health centers, and 34.8% had POD24 with first-line chemoimmunotherapy.

The CR rate and ORR for all patients (third-line therapy or later) were 24.7% and 64.9%, respectively. Median (95% CI) DOR and TTNT-D were 13.1 (12.0–16.2) months and 16.3 (13.6–18.4) months, respectively. Median (95% CI) PFS and OS were 12.6 (11.5–13.9) months and 56.8 (48.2–76.6) months, respectively. These outcomes worsened with each successive therapy. Compared with those receiving their third-line therapy (n=218), those receiving their fourth-line therapy (n=91) or fifth-line or later (n=67) had a lower CR rate (third-line: 28.4%; fourth-line: 24.2%; fifth-line or later: 13.4% and ORR (third-line: 70.6%; fourth-line: 60.4%; fifth-line or later: 52.2%), with shorter median (95% CI) TTNT-D (third-line: 18.8 [16.1–23.4] months; fourth-line: 13.1 [11.2–19.1] months; fifth-line or later: 9.8 [6.0–15.9] months), PFS (third-line: 13.2 [12.2–19.9] months; fourth-line: 12.2 [9.8–18.0] months; fifth-line or later: 8.1 [5.2–13.8] months), and OS (third-line 82.7 [54.3–111.0] months; fourth-line: 54.8 [43.5–79.4] months; fifth-line or later: 32.2 [23.4–41] months).

Outcomes were worse for patients ≥65 years of age (n=221) than those <65 years of age (n=155), with a lower CR rate (21.7% vs 29.0%) and ORR (62.9% vs 67.7%), and shorter median (95% CI) OS (49.2 [40.7–58.4] months vs 85.1 [54.3–117.5] months; P=0.0107). Compared with patients with low- or intermediate-risk FLIPI scores (n=141), patients with high-risk FLIPI scores (n=95) had a lower CR rate (14.7% vs 28.4%) and ORR (58.9% vs 73.0%) and shorter median (95% CI) DOR (12.0 [7.5–17.3] months vs 16.8 [13.0–21.5] months), TTNT-D (13.0 [10.0–17.6] months vs 20.3 [15.9–25.5] months), PFS (12.2 [8.4–13.2] months vs 15.3 [12.2–26.7] months), and OS (36.8 [27.1–52.8] months vs 58.2 [43.5–117.5] months; P=0.005).

No notable differences in outcomes were observed with respect to patients with early relapse, or POD24 with first-line chemoimmunotherapy. However, compared with patients with non- double-refractory disease (n=185), patients with double-refractory disease (n=191) had less favorable outcomes, with a lower CR rate (22.0% vs 27.6%) and ORR (61.8% vs 68.1%), and shorter median (95% CI) DOR (11.4 [8.2–14.2] months vs 17.0 [12.7-21.4] months), TTNT-D (13.2 [11.9–15.0] months vs 20.3 [16.4–25.4] months), PFS (10.9 [8.7–12.7] months vs 18.6 [12.3–28.6] months), and OS (43.1 [32.0–56.1] months vs 85.1 [56.8–132.3] months; P<0.0001).

Compared with patients initiating therapy in 2019 or earlier, those initiating therapy in 2020 onward had substantially shorter 24-month OS estimates (75.3% vs 63.3%). Further, a greater average annual death rate occurred during the COVID-19 pandemic (2020-2022: 11.8%) than prior to COVID (2012–2020: 4.4%).

2.4.1. Assessment of proposed post authorisation confirmatory trial as SOB

The adequacy of the Phase 3 Study M20-638 to fulfil the requirements as a confirmatory study was previously discussed during the scientific advice that had been received on 15th Sep 2022 (EMA/SA/0000095173). Regarding the rationale of the addition of epcoritamab to R2, the MAH argued that the combination therapy of lenalidomide plus rituximab is chosen as in comparison to rituximab monotherapy for this combination therapy higher and improved median PFS, have been reported. The rationale for the combination of epcoritamab with R2 is to harness the synergy between the enhanced immunomodulation with lenalidomide, rituximab, and T-cell engagement by epcoritamab to increase the depth and rate of response. The use of epcoritamab in combination with lenalidomide and of epcoritamab in combination with rituximab is supported by non-clinical data. Further, preliminary clinical data indicate that epcoritamab in combination with R2 is associated with fast depletion of B cells and a reduction in inflammatory cytokine peak levels as compared to epcoritamab monotherapy. The proposed regimen of epcoritamab plus R2 in the experimental arm is considered acceptable. The study will be conducted in earlier line of treatment than the indication that is currently applied for. Further in this study epcoritamab will be used in combination therapy whereas for patients with R/R FL who received 2 or more lines of systemic therapy, epcoritamab will be used as monotherapy. Given these differences, with the proposed confirmative study, no conclusions can be drawn about the exact magnitude of the clinical benefit of epcoritamab for the currently applied indication. However, if with this RCT a significant and clinically relevant benefit regarding PFS and OS for epcoritamab + R2 in comparison to R2, this would be reassuring also for the benefit of epcoritamab in later lines of treatment, therefore it is considered that this study could fulfil the need for a confirmatory study. The study was initiated with the First Subject First Visit in September 2022.. The planned completion date (Last Subject Last Visit) is in June 2030. As study recruitment is already started, given the number of participating study sites and the currently enrolled patients, completion of the study might be expected within a reasonable time frame. In addition, the final CSR, including final efficacy and safety data for FL patients of both the iNHL expansion cohort and the FL optimization cohort of study the GCT3013-01 will be provided. In conclusion, it is likely that the MAH will be able to provide comprehensive data.

2.4.2. 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 FL in the EU supporting the demonstration of major therapeutic advantage is shown in Table 25 and Table 26 below.

Table 25: Comparison Background Patient Population for Subjects with FL Enrolled in the GCT3013-01 Trial (Epcoritamab) vs Pivotal Clinical Trials of Most Recent Therapies

Drug Name	Epcorit-amab[a]	R[2b] AUGMENT	R[2b] MAGNIFY[#]	BR[c]	G-B[d]	Ibritu-momab[e]	Idelali-sib[f]	Duveli-sib[g]	Axi-cel[h]	Tisa-cel[i]	Mosu[j]	Zanu+Obi[k]
Background Patient Population												
N	128	178 (147 FL)	394 (318 FL)	114 (58 FL)	194	57	125	129 (83 FL)	122	94	90	145
Median age (range)	66 (39-84)	64 (26-86)	66 (35-91)	68.5 (59-74)	63 (NL)	54 (34-73)	64 (33-87)	65 (30-90)	60 (34-79)	57 (29-73)	60.0 (29-90)	63.0 (31–84)
Age ≥ 65 years, %	52.3	46	NL	38[c]	NL	NL	44.8	50	30	25.5	31.1	42.8
Number of prior LOT:												
1	0	57	NL	66	44	NL	0	12.0	2	0	0	0
2	36.7	17	NL	20	34	NL	26.4	22.9	35	25.5	37.8	44.8
≥ 3 (3, > 3)	63.3 (32.0, 31.3)	25	NL	14	NL	NL	73.6 (15.2, 58.4)	57.8	61 (25, 36)	74.4 (20.2, 54.2)	62.2 (31.1, 31.1)	55.2 (26.9, 28.3)
Median prior LOT (range)	3 (2-9)	1 (1-12)[b]	2	1 (1-2)	2 (1-10)	4 (1-9)	4 (2-12)	3 (1-10)	3 (1-10)	4 (2-13)	3 (2-10)	3 (2–11)
Refractory to last LOT (%)	69	17	NL	4	92	NL	NL	96	NL	78.7	68.9	32.4
Double refractory to anti-CD20 and alkylating agent (%)	70	NL	22	NL	79	NL	NL	NL	30	69.1	53.3	NL
FLIPI 3-5 (%)	61	39	NL	43	40	19	NL	65.1 (from 83 FL)	42	60.6	44.4	53.1
POD24	52.3	NL	NL	NL	NL	NL	NL	75	54	64.9	52.2	34.5

axi-cel = axicabtagene ciloleucel; BR = bendamustine and rituximab; CHMP = Committee for Medicinal Products for Human Use; COD = cutoff date; CR = complete response; EMA = European Medicines Agency; EMEA = European Medicines Evaluation Agency; EU = European Union; FL = follicular lymphoma; FLIPI = Follicular Lymphoma International Prognostic Index; G-B = obinutuzumab and bendamustine; iNHL = indolent non-Hodgkin lymphoma; IRC = independent review committee; IWG = international working group; LOT = line of therapy; mosu = mosunetuzumab; MZL = marginal zone lymphoma; NL = not listed; Obi = Obinutuzumab; ORR = overall response rate; POD24 = progression of disease within 24 months; R2 = rituximab and lenalidomide; SLL = small lymphocytic lymphoma; SmPC = Summary of Product Characteristics; tisa-cel = tisagenlecleucel; zanu = zanubrutinib.

a. From GCT3013-01 iNHL expansion cohort (128 subjects with FL 1-3A in the pivotal iNHL expansion cohort of Study GCT3013-01, DCO: 21 April 2023). Source: Table 14.1.1.2, Table 14.1.1.3, and Table 14.1.1.6.1.

b. Data for AUGMENT study were obtained from Leonard et al. 2019.[5] Background patient population was based on 178 subjects in the iNHL cohort with 147 subjects with FL (83%) and 31 subjects with MZL (17%). The number of median prior lines was based on the total number of subjects enrolled (N = 359; R^2 and rituximab+placebo groups).[5] Note: 56% of subjects enrolled in the AUGMENT study had only 1 line of prior anti-lymphoma treatment. In addition, subjects enrolled in the AUGMENT study were eligible to receive rituximab monotherapy.
#Data for MAGNIFY study were obtained from Lansigan, 2022.[6] The number of subjects with double refractory were obtained from Lansigan, 2022.[7]

c. From Rummel et al. 2016.[8] Responses and background patient population were based on 58 subjects with FL (51%) from the 114 subjects in the iNHL cohort. Thirty-eight percent of subjects were > 70 years.[8]

d. Obinutuzumab (Gazyvaro) SmPC was used as a source for efficacy analysis and background patient population. ORR and CR were IRC assessed using 2007 IWG.[9] Background patient population was based on 194 subjects with iNHL with 81.1% of subjects with FL.

e. From demographic data and baseline disease status as listed in Study 106-06 for ibritumomab tiuxetan (Zevalin), as listed in Table 3 of Kymriah Orphan Maintenance Assessment Report (EMA/OD/0000054173).

f. From background patient population of 125 subjects with iNHL including 72 subjects with FL, 28 subjects with SLL, 10 subjects with lymphoplasmacytic lymphoma/Waldenstrom macroglobulinaemia, and 15 subjects with MZL, Table 32 and 33 of idelalisib (Zydelig) assessment report (EMA/CHMP/511776/2014).

g. Duvelisib (Copiktra) SmPC was used as a source for background patient population based on 129 subjects (83 FL, 28 SLL, and 18 MZL), except for % of patients with FLIPI 3-5 were obtained from the assessment report based on 83 subjects with FL (EMA/CHMP/236249/2021).

h. Axicabtagene ciloleucel (Yescarta) SmPC was used as a source for background patient population of all 122 subjects with FL (Full Analysis Set). The numbers for subjects with prior LOT and FLIPI 3-5 were obtained from Table 8 of the axicabtagene ciloleucel (Yescarta) assessment report (EMA/622447/2022).

i. Tisagenlecleucel (Kymriah) SmPC was used as a source for background patient population based on the efficacy analysis set.

j. From background patient population of 90 subjects with FL in B11 Expansion, Table 19 of mosunetuzumab (Lunsumio) Assessment Report (EMA/CHMP/63179/2022).

k. From background patient population of 145 subjects with FL in Study BGB-3111-212, Table 13 of zanubrutinib (Brukinsa) Assessment Report (EMA/CHMP/510757/2023).

Note: A positive CHMP opinion was issued on 28 January 2022 for lisocabtagene maraleucel (Breyanzi) for the treatment of adult patients with R/R DLBCL, primary mediastinal large B-cell lymphoma, and FL Grade 3B, after 2 or more lines of systemic therapy. FL Grade 3B is typically included as an aNHL subtype so Breyanzi was not included as a treatment for comparison.

Table 26: Efficacy Comparison of Epcoritamab vs Most Recent Therapies for R/R FL

Drug Name	Epcoritamab[a] APR 2023 DCO	Epcoritamab[a] OCT 2023 DCO	R[2b] AUGMENT	R[2b] MAGNIFY[#]	BR[c]	G-B[d]	Ibritumomab[e]	Idelalisib[f]	Duvelisib[g]	Axicel[h]	Tisacel[i]	Mosu[j]	Zanu+Obi[k]
Approval Type	NA		Full		NA	Full	Full	Full	Full	Full	Full	Conditional	Full
MoA	Bispecific Ab		Immunomodulatory		Chemoimmunotherapy	Chemoimmunotherapy	Radioimmunotherapy	PI3K inhibitor	PI3K inhibitor	CAR T	CAR T	Bispecific Ab	BTK inhibitor
RoA	SC		IV		IV	IV	IV	PO	PO	IV	IV	IV	PO
Efficacy analysis:													
Response evaluable set (N)	128	128	147 (67)	318 (115)	114 (58 FL)	155 (79)	54	72	73	122	94	90	145
ORR %	82	82.8	81	57	82	75	74	55.6	40	92	86.2	80.0	69.0
CRR %	62.5	63.3	34	13	40	20	15	16.7	0	77	69.1	60.0	39.3
Median DOR (months)	NR	23.6	NR	5.1	NL	NR	6.4	11.8	10.0	38.6	NR	22.8	NR
Median PFS (months)	15.4	15.4	39.4	50.5	34.2	NR	6.8	11.0	NL	40.2	18.4	17.9	28.0
Median OS (months)	NR	NR	NL	NL	109.7	NR	NL	NR	NL	NL	NL	NL	NR
Median duration of study follow-up (months)	17.4	22.9	28.3	40.6	96	22	NL	NL	NL	25.9	18.6	18.3	18.3

Ab = antibody; axi-cel = axicabtagene ciloleucel; BR = bendamustine and rituximab; CAR T = chimeric antigen receptor T-cell therapy; COD = cutoff date; CR = complete response; DOR = duration of response; FL = follicular lymphoma; G-B = obinutuzumab and bendamustine; iNHL = indolent non-Hodgkin lymphoma; IRC = independent review committee; IV = intravenous; IWG = international working group; IWRC = International Workshop Response Criteria; MoA = mechanism of action; mosu = mosunetuzumab; NA = not applicable; NL = not listed; NR = not reached; Obi = obinutuzumab; ORR = overall response rate; OS = overall survival; PO = orally; PFS = progression-free survival; R2 = rituximab and lenalidomide; RoA = route of administration; R/R = relapsed/refractory; SC = subcutaneous; SmPc = Summary of Product Characteristics; tisa-cel = tisagenlecleucel; zanu = zanubrutinib.

a. From GCT3013-01 iNHL expansion cohort (128 subjects with FL 1-3A in the pivotal iNHL expansion cohort of Study GCT3013-01, DCO: 21 April 2023 or 16 October 2023). Responses were based on ORR and CR rate, IRC Assessment per Lugano criteria.[10] Source: Table 14.2.1.1.1, 14.2.1.7.1, Table 14.2.1.12.1, and Table 14.2.1.17.

b. ORR, CRR, and DOR were from subgroup population of subjects with ≥2 prior LOT (N = 67), as described in the Tazverik (tazemetostat) NDA 213400 multidisciplinary review. The ORR, CRR, and DOR from overall population (N = 147 subjects with FL from a total of 178 subjects from the iNHL cohort) as described in Leonard et al. 2019[5] were 80%, 35%, and 36.6 months respectively. ORR and CR were IRC assessed using 2007 IWG.[9] The other efficacy data were obtained from Leonard et al. 2019[5] Note: 56% of subjects enrolled in the AUGMENT study had only 1 line of prior anti-lymphoma treatment. In addition, subjects enrolled in the AUGMENT study were eligible to receive rituximab monotherapy.

#ORR, CRR, and DOR were from subgroup population of subjects with ≥ 2 prior LOT (N = 115), as described in the Tazverik (tazemetostat) NDA 213400 multidisciplinary review. The ORR, CRR, and DOR from the overall population from MAGNIFY study (N = 394 subjects with 318 subjects [81%] were FL Grade 1-3a) as listed from Lansigan, 2022 were 71%, 42%, and NR (95% CI: 43.9-NR).[6] The other efficacy data were obtained from the Lansigan, 2022.[6]

c. Rummel et al. 2016.[8] Responses and background patient population were based on 114 subjects in the iNHL cohort with 58 FL subjects (51%).[8]

d. ORR, CRR, and DOR were from subgroup population of subjects with ≥2 prior LOT (N = 79), as described in the Tazverik (tazemetostat) NDA 213400 multidisciplinary review. The ORR, CRR, and DOR from overall population (N = 155) as described in the overall population as described in the Obinutuzumab (Gazyvaro) SmPC were 79.7%, 15.7%, and NR. Gazyvaro SmPC was used as a source for the other efficacy analysis. ORR and CR were IRC assessed using 2007 IWG.[9] Background patient population was based on 194 subjects with iNHL with 81.1% of subjects with FL.

e. From demographic data and baseline disease status as listed in Study 106-06 for ibritumomab tiuxetan (Zevalin), as listed in Table 3 of Kymriah Orphan Maintenance Assessment Report (EMA/OD/0000054173). ORR and CR were assessed by an independent panel of radiologists and oncologists (LEXCOR) according to IWRC.[11]

f. Idelalisib (Zydelig) SmPC was used as a source for efficacy analysis. ORR and CR were IRC assessed using 2007 IWG.[9] Assessment Report was used as a source for the background patient population. Background patient population data was from the full analysis set (125 subjects with iNHL).

g. Duvelisib (Copiktra) SmPC was used as a source for efficacy analysis. ORR and CR were IRC assessed using 2007 IWG.[9]

h. From summary of key efficacy results of all subjects with FL (Full Analysis Set), as listed in Table 9 in axicabtagene ciloleucel (Yescarta) assessment report (EMA/622447/2022).ORR and CR were IRC assessed per IWG Lugano classification.[10]

i. Tisagenlecleucel (Kymriah) SmPC was used as a source for efficacy analysis where available, except the median PFS and OS data were obtained from the assessment report (EMA/211805/2022). ORR and CR were IRC assessed per IWG Lugano classification.[10]

j. Mosunetuzumab (Lunsumio) SmPC was used as a source for efficacy analysis where available. ORR and CR were IRC assessed using 2007 IWG.[9]

k. Zanubrutinib (Brukinsa) SmPC was used as a source for efficacy analysis where available. Responses were based on ORR and CR rate, IRC assessment per Lugano criteria.[10]

Note: A positive CHMP opinion was issued on 28 January 2022 for lisocabtagene maraleucel (Breyanzi) for the treatment of adult patients with R/R DLBCL, primary mediastinal large B-cell lymphoma, and FL Grade 3B, after 2 or more lines of systemic therapy. FL Grade 3B is typically included as an aNHL subtype so Breyanzi was not included as a treatment for comparison.

h. From summary of key efficacy results of all subjects with FL (Full Analysis Set), as listed in Table 9 in axicabtagene ciloleucel (Yescarta) assessment report (EMA/622447/2022).ORR and CR were IRC assessed per IWG Lugano classification.[29]

i. Tisagenlecleucel (Kymriah) SmPC was used as a source for efficacy analysis where available, except the median PFS and OS data were obtained from the assessment report (EMA/211805/2022). ORR and CR were IRC assessed per IWG Lugano classification.[27]

j. Mosunetuzumab (Lunsumio) SmPC was used as a source for efficacy analysis where available. ORR and CR were IRC assessed using 2007 IWG.[31]

Breyanzi (lisocabtagene maraleucel [liso-cel]) was approved by the EC on 04 April 2022 for the treatment of adult patients with R/R DLBCL, PMBCL, and FL3B, after two or more lines of systemic therapy. FL Grade 3B resembles DLBCL from morphologic and genetic perspectives and was reclassified in the 5th edition of the WHO classification of haematolymphoid tumours as follicular large B-cell lymphoma. In clinical practice, as well as in clinical studies, it is commonly managed similarly to DLBCL according to the MAH. As a result, the MAH does not consider that liso-cel is relevant to clinical practice for R/R FL Grade 1–3A in the EU and considered that a comparison of epcoritamab to liso-cel was not warranted. MTA is however discussed in Section 3.7.3.

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The pivotal study population in this application is the iNHL cohort (including FL Grade 1-3A) of the expansion phase of the GCT3013-01 study. The escalation phase of this study was used for dose finding. The FL cohort of the optimization part of Study GCT3013-01, the FL cohort of GCT3013-04 study in Japanese subjects and a real world evidence study are presented as supportive studies.

GCT3013-01 study is a 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. The trial includes a Dose Escalation Part, an Expansion Part and an Optimization Part. The expansion part is considered to be the pivotal study by the MAH. The aim of the Expansion Part of this trial was to evaluate the efficacy and safety of epcoritamab using the RP2D regimen as determined by the escalation part of the study. The Expansion Part of the trial was initiated with parallel enrollment in 3 cohorts of subjects with distinct B-cell lymphoma subtypes: R/R aNHL cohort (LBCL), R/R iNHL cohort (including FL Grade 1-3A), and R/R MCL cohort who were treated with the RP2D of epcoritamab.

The iNHL Expansion Part was conducted in 2 stages. In Stage 1, only subjects with R/R FL Grade 1-3A were enrolled in the iNHL cohort (N=33), for who response data was collected. Following an interim

futility analysis, additional subjects with iNHL could be enrolled for Stage 2, including subjects with other iNHL subtypes (i.e., SLL, MZL). The study was to proceed to stage 2 if, in stage 1, there were more than 15 responders out of 30 response evaluable subjects based on investigator assessment. Based on results from the interim futility analysis, an additional 95 subjects with FL Grade 1-3A were to be enrolled to Stage 2, along with up to 30 subjects with other types of iNHL (MZL and SLL). In total, up to 158 subjects were to be enrolled in iNHL.

From the documents provided it is not fully clear whether the number of subjects that would be included after the interim futility analysis was pre-specified (n=95) as it is only included in the last version of the SAP (mid 2023). The impact of the selection adaptive element (i.e. interim decision to continue the study) on the estimation of the ORR (and DOR) was analysed. The interim bias does not meaningfully affect the overall estimate for ORR, CR, and median DoR.

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 (EMA/CHMP/564424/2021).

Scientific advice (EMEA/H/SA/4478/2/2020/III) was requested for the pivotal study and proposed confirmatory study. The MAH largely adhered to the advice.

The primary estimand is ORR regardless of treatment discontinuation while not using subsequent anti-lymphoma therapies. This is acceptable. However, this estimand is estimated only in subjects that used at least one dose of epcoritamab, hence is in principle not comparable to the definition of ORR in "all randomised" set in a randomised design.

For sample size calculation the null hypothesis was that the ORR for the FL Grade 1-3A group was at most 50%, and the alternative hypothesis was that the ORR is at least 65%. The sample size/power estimation was based on 128 subjects in the FL 1-3A group, with 30 additional subject to be included in the total iNHL cohort. With 128 FL subjects enrolled in the iNHL cohort and with one sample binomial test, this provided approximately 90% power to reject the null hypothesis with a two-sided significance level of 0.05.

For the FL subgroup of the iNHL cohort, patients need to have histologic confirmed FL grade 1, 2 or 3A at initial diagnosis without clinical or pathological evidence of transformation.

All patients had relapsed or refractory disease to the last prior line therapy and previously treated with at least 2 lines of systemic antineoplastic therapy including at least 1 anti-CD20 monoclonal antibody–containing therapy and an alkylating agent or lenalidomide-containing therapy. 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. The eligibility criteria are considered acceptable to select the target population.

In order to be included in study GCT3013-01, patients need to have documented CD20+ mature B-cell neoplasms based on representative pathology report. CD20-positivity was based on a representative pathology report but at time of screening histopathological testing to confirm CD20-positive FL 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 whereas, level of CD20 expression might impact response to epcoritamab.

The posology was investigated in the escalation part of the GCT3013-01 study. The RP2D regimen selected for the expansion part was based on the escalation part. In the EMEA/H/C/005985/0000 procedure (EPAR EMA/CHMP/419797/2023 d.d.20 July 2023) the choice of 0.16 mg/0.8 mg/48 mg as

the RP2D was considered acceptable, while it was noted that it is uncertain whether the most optimal dose has been selected. Subjects were premedicated with corticosteroids, antihistamines, and antipyretics prior to the first 4 doses of epcoritamab. For subsequent doses of epcoritamab, premedication and CRS prophylaxis were optional. If CRS ≥ grade 2 occurred following the fourth epcoritamab administration (first full dose) 4-day consecutive corticosteroids were to be repeated until 1 full epcoritamab dose was administered without subsequent occurrence of CRS of any grade. Other concomitant medications were allowed to provide adequate subject care and were given as clinically indicated, except for anti-lymphoma therapy. Starting from amendment 9 in the GCT3013-01 study additional measures for sufficient fluid intake were recommended as well as other measures to reduce CRS (refer to safety section).

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 continued dosing was part of the studied regimen, it is not possible to conclude on optimal duration of treatment and whether or not it might be possible to stop treatment or have a treatment holiday, before disease progression.

The primary endpoint of the study is ORR, defined as the proportion of subjects who achieve best overall response (BOR) of partial response (PR) or complete response (CR) assessed by IRC per Lugano criteria. Subjects who achieved a PR or CR after a PD (Lugano) or IR (LYRIC) assessment were considered responders for the purposes of ORR. The Lugano criteria with PET scans, 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. Two definitions of DOR were used in the analysis, where the primary definition of DOR accounted for subsequent anti-lymphoma therapy and censored DOR at the last adequate tumor assessment on or prior to the date of subsequent anti-lymphoma therapy, while the secondary definition of DOR did not account for subsequent anti-lymphoma therapy. Other key secondary efficacy endpoints included CR rate, DOCR, PFS, TTR, TTCR, OS, TTNT, and rate of MRD negativity. Efficacy evaluations were conducted as specified in the visit assessment schedule of the protocol, and included the following: scheduled imaging assessments during Weeks 6, 12, 18, 24, 36, 48, and then every 24 weeks thereafter.

Overall, the objectives and endpoints are considered appropriate for a phase 2 single-arm trial, and of clinical relevance. For the response evaluations after 24 weeks, the time between assessments is increased from every 6 weeks to every 12 weeks and after 48 weeks to every 24 weeks. Sensitivity analyses were conducted to determine whether the long period between assessments may bias the estimated duration of response, PFS and TTNT, upwards. These analyses show no major impact on the results of the time to event endpoints.

The amendments and protocol deviations are not expected to have a significant impact on the efficacy results of the FL cohort even though amendments 7-9 were dated after start of the expansion part of the study.

Historical control data was submitted to contextualize study results with available treatment options. Comparison of historical control data with trial data should be interpreted with caution, given potential differences in patient base line characteristics, disease history, and received treatments (both anti-tumour treatment and supportive care) (EMA/CHMP/564424/2021).

Further, the MAH provided indirect treatment comparisons of the epcoritamab study results vs study results of currently available therapies in r/r FL patients after at least two systemic therapies. As the source trials for these indirect comparisons were all single arm trials or retrospective cohorts, these comparisons lack a common control (‘unanchored’) which means that the underlying assumption is that outcomes considered are fully predictable from the covariates measured and used in these indirect

comparisons. Moreover, only aggregate summary data was available for the comparators, so the correction is only on sample averages. Notable differences in inclusion and exclusion criteria of these trial were identified, including differences in age of the subjects, previous lines of therapy, rate of patients with double refractory disease (i.e. refractory to an anti-CD20 containing regimen and an alkylator), FLIPI ≥3, and time that the studies were conducted. Analyses were conducted for the overlapping patient populations represented in the epcoritamab trial and comparator trials, for the response rates. Response rates were compared for and after adjusting/weighting and matching trial cohorts based on distribution of key demographic and clinical variables such as age, sex, ECOG score, disease stage, FLIPI, number of prior lines of therapy, prior stem cell transplantation, progression of disease within 24 months (POD24), double refractory disease, refractory to last line of therapy and LDH. Except for the comparison with tisa-cel, no indirect comparisons could be corrected for LDH; the indirect comparisons with chemo-immunotherapy and axi-cel could not be corrected for being double refractory. Whereas MAICs could be conducted for response rates using individual patient data from GCT3013-01 and comparator trials, indirect comparisons of DOR or DOCR were not possible because the baseline characteristics of responders and complete responders from comparator trials were not publicly available.

Although the effort of the MAH to contextualize efficacy results of the FL cohort with currently available therapies and historical controls is appreciated, it is considered that the incidence of FL may have allowed for an (underpowered) comparative trial, and even underpowered RCT study would provide more robust demonstration of benefit than a single arm trial. However, in this setting with high unmet need precedent exists for approval based on single arm trials when tumour activity with durable responses is compelling.

Efficacy data and additional analyses

FL expansion cohort of the GCT3013-01 study

As of the data cutoff date of 21 April 2023, a total of 224 subjects were enrolled and 155 subjects received at least 1 dose of epcoritamab in the iNHL Expansion Part. Sixty-nine subjects appear to be not eligible. Of the 155 subjects who received at least 1 dose of epcoritamab, 128 subjects were diagnosed with FL Grade 1-3A and 27 subjects with other iNHL subtypes (i.e., MZL and SLL).

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.

Generally, the baseline data of the FL cohort reflect a R/R FL population after multiple systemic therapies (at least 2), however very few patients (n=7) with ECOG 2 were included. One subject was enrolled as FL but was found to have transformed DLBCL after study entry. This subject is included in the FL FAS.

The median age of subjects with FL was 65.0 years. Of note, 67 (52.3%) subjects were ≥65 years old, and 17 (13.3%) subjects were ≥75 years old. Twenty-two (17.2%) subjects had moderately impaired baseline renal function. Hepatic function at baseline was normal for 107 (83.6%) subjects.

Forty-one subjects (32.0%) had FL Grade 3A disease; 109 (85.2%) of the subjects had advanced stage lymphoma (Ann Arbor Stage III and IV disease); 78 (60.9%) subjects had a FLIPI score ≥3. Approximately two thirds of subjects (90 [70.3%]) were double refractory to an anti-CD20 and alkylating agent, and 67 (52.3%) subjects had POD24 from any first line therapy. The median number of prior lines of systemic anti-lymphoma therapy was 3.0 (range: 2, 9); 40 (31.3%) subjects received 4 or more prior lines of therapies. Patients who received prior CAR-T therapy within 30 days prior to

first epcoritamab administration, were excluded per exclusion criterium. Six subjects (4.7%) in the FL group of the iNHL expansion cohort in study GCT3013-01 had received prior CAR-T therapy.

The primary endpoint ORR (CR + PR) in the FAS population (n=155), was 82.6%, with 97 subjects having a CR (62.6%). The median DOR was 21.4 months (95% CI 14.0, NR).

In subjects with FL the ORR was 82.0% (95% CI: 74.3, 88.3), with 80 (62.5%) and 25 (19.5%) subjects achieving best responses of CR and PR, respectively.

In the updated clinical DCO of 16 October 2023, the primary efficacy endpoint of ORR based on IRC assessment determined by Lugano criteria was 82.8% (95% CI: 75.1, 88.9) in subjects with FL, with 81 (63.3%) and 25 (19.5%) subjects achieving best responses of CR and PR, respectively.

The ORR results were generally consistent between the different predefined subgroups. However, numerically lower ORR rates are noted in patients who had received 4 or more prior lines of therapy, patients with relative short time from last therapy till first dose of epcoritamab, patients refractory to most recent prior therapy and patients who received prior rituximab+lenalidomide. Point estimated ORRs for all subgroups were 63% or above and these responses might still be clinically relevant for heavily pretreated patients. However, it is noted that also poorer response rates were observed in patients with shorter time from last anti-CD20 therapy till first dose of epcoritamab, and in patients refractory to their most recent prior anti-CD20 containing therapy (which could have been in an earlier line than the last prior therapy). Further, data showing CD20 expression levels by BOR category, indicate potentially poorer results in patients with low CD20 expression. A warning in the SmPC regarding the lack of information on efficacy in patients with low CD20 expression, similar to what was included for the DLBCL indication was added.

Among the subjects with FL who achieved PR or CR (n=105), the median follow-up for DOR analysis was 14.8 months (range: 0.0+, 27.2+). At the data cut of date, the median DOR was not reached (NR) (95% CI: 13.7, NR). A high number of patients were censored (for FL cohort 65.7%), mainly due to "clinical cutoff". The estimated percentage of subjects remaining in response at 12 and 18 months was 68.7%, and 58.4%, respectively.

For patients with FL, the median DOR by secondary definition, i.e. not censoring for new anticancer therapy, was reached at 21.4 months (95% CI: 13.3, NR). The 12-month estimate of patients remaining in response, using secondary definition, was 66.5% (95% CI: 55.9, 75.2).

Updated DOR, with a DCO of 16 October 2023 for subjects with FL based on the primary definition (accounting for subsequent anti-lymphoma therapy and censoring DOR at the last adequate tumour assessment on or prior to the date of subsequent anti-lymphoma therapy) and secondary definition (not accounting for subsequent anti-lymphoma therapy) was respectively; 23.6 months [95% CI: 13.8, NR]) and 21.4 months [95% CI: 13.7, NR]. These DOR results are considered clinically relevant and sufficient to support the positive ORR results of epcoritamab in the GCT3013-01 iNHL expansion cohort.

For patients (FAS) with reported CR median DOCR was not reached (NR) (95% CI: 21.4, NR), after a median DOCR follow-up of 14.8 months (range: 9.9, 15.1). For FL patients who had a CR to epcoritamab treatment, median DOCR was not reached (NR) (95% CI: 21.4, NR), after a median DOCR follow-up of 14.8 months (95% CI 10.0, 15.2). The median DOCR based on IRC Assessment, Lugano Criteria with the primary definition and secondary definition was also NR based on DCO 16 October 2023.

A sensitivity analysis where new anti-lymphoma therapy administration is considered as an event and time to administration is considered as event time, was conducted. For this sensitivity analysis the median DOR (as assessed by the IRC using Lugano criteria) for subjects with FL in the iNHL expansion

cohort was 20.7 months (95% CI: 12.2, NR), which is slightly shorter than the updated DOR results per primary and secondary definition, however still considered supported for the positive ORR results.

The median PFS in the FAS population was 16 months (95% CI 13.6, NR). Among subjects with FL, the median PFS (primary definition), after a median follow-up of 16.1 months (range: 0.0+, 28.8+), was 15.4 months (95% CI: 10.9, NR). Median OS for the FAS population and subjects with FL was not reached (NR, 95% CI NR, NR). Also median TTNT for the FAS population and for the subjects with FL was not reached (NR, 95% CI, NR, NR; NR, 95% CI NR, NR, respectively).

For the updated data of the DCO of 16 October 2023, median PFS was 15.1 months (95% CI: 9.5, NR), with estimated percentage of subjects remaining in response at 12 and 18 months of 57.5% and 47.9%, respectively. At that time with a median OS follow-up of 22.9 months, the median OS was NR (95% CI: NR, NR). The estimated percentage of subjects who remained alive at 12 and 18 months was 81.9% and 71.2%, respectively.

Time-to-event endpoints cannot be adequately assessed in uncontrolled studies.

DOR, PFS and OS results might be (negatively) influenced by the COVID-pandemic. Sensitivity analyses were performed to evaluate the impact of COVID-19 on efficacy results in the FL population showing longer DOR, PFS ad OS after adjustment for COVID-19 deaths.

For the FAS population and for subjects with FL, the median TTR based on IRC assessment was 1.4 months (range:1.0, 4.3 and 1.0, 3.0, respectively). For the subjects with FL, the median TTCR based on IRC assessment was 1.5 months (range: 1.2, 11.1). This correlates to the first postbaseline disease assessment, indicating response was generally achieved early with epcoritamab treatment. With the DCO 16 October 2023, the median TTNT was NR (95% CI: 26.5, NR). The estimated percentage of subjects not initiating subsequent therapy at 12 and 18 months was 66.3% and 62.4%, respectively.

The rate of MRD negativity at any timepoint in MRD evaluable subjects with FL (N=91) was 67.0% (95% CI: 56.4, 76.5). With a median follow-up of 8.1 months, the median duration of MRD negativity was 16.5 months (95% CI: 10.8, NR). A total of 5 (3.9%) subjects with FL received a subsequent allogeneic HSCT. The rate of MRD negativity at any timepoint using the PBMC analyte at a threshold of 10-6 in MRD evaluable subjects with FL (n = 93) was 65.6%.

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

The analyses of the used PROs for determination of quality of life are difficult to interpret in a single arm trial. Generally it seems that by the FACT-Lym and EQ-5, while on treatment, there was no deterioration in the symptoms and quality of life (QoL) experience, consistent with their QoL being maintained. The compliance rate for the FACT-LYM PRO was >75% at most time points.

FL optimization cohort of the GCT3013-01 study

In addition to the efficacy results of GCT3013-01 of FL patients treated in the expansion part of the study, efficacy results from the optimization part of study GCT3013-01, were included in the original submission. At that time, the optimization part included in total 36 FL patients, of which 30 FL patients in Arm A, who were treated with the proposed 3-step step-up-dosing.

Only patients with FL Grade 1-3A were enrolled in the FL 1-3A cohort of the optimization part, otherwise inclusion and exclusion criteria were the same as for the iNHL expansion cohort. The baseline characteristics in the FL optimization cohort were generally similar to those in the expansion cohort, though a few baseline characteristics may appear more favorable in the optimization part, notably 0% versus 5.5% ECOG 2 patients, 46.7% versus 60.9% patients with FLIPI ≥3, median 2 (range: 2-7) vs 3 (2, 9) prior LOT, 36.7% versus 54.7% refractory to ≥2 consecutive LOT, and 60%

versus 68.8% refractory to the last LOT in Arm A of the FL optimization cohort versus the FL patients in the iNHL expansion cohort.

The ORR in subjects in Arm A was 83.3% (95% CI: 65.3%, 94.4%), CR rate was 56.7% (95% CI: 37.4%, 74.5%) and PR rate was 26.7%. Response rates were comparable to the efficacy results for FL patients obtained in the expansion part of the study. For the FL indication a new posology is introduced in the SmPC based on an unplanned analysis from the FL optimization cohort. Reported response rates appear to be comparable, but due to the small sample size (N=30) at the time of the original submission, it was not possible to conclude on similar efficacy for the different dosing regimens. However, since exposure was lower following the 3rd and 4th epcoritamab administration but comparable to the 2-step-up dosing regimen thereafter, the 3-step-up dosing regimen was not expected to impact efficacy (refer to safety discussion).

It was noted that from stage 1 to stage 3 of the optimization trial, a total of approximately 80 patients could be enrolled for Arm A, given that only this arm was chosen for stage 3. The results for 30 patients in Arm A had been provided in the original submission, with a DCO of 31-June-2023 and a median duration of study follow-up of 3.9 months (range: 1.9, 8.7). On request of the CHMP, updated efficacy results were submitted. The ORR based on investigator assessment by Lugano criteria in subjects in Arm A of the FL optimization cohort (n=86) as of the DCO of 08 January 2024 was 86.0% (95% CI: 76.9, 92.6), and the CR rate was 64.0% (95% CI: 52.9, 74.0). Among the subjects in Arm A of the FL optimization cohort who achieved PR or CR (n= 74), the median DOR follow-up was 2.8 months. The median DOR based on investigator assessment per primary definition was NR (95% CI: NR, NR). DOR results per secondary definition were consistent with those of the primary definition.

Results of response analysis for pooled FL patients, were submitted. Response rates in the FL optimization cohort using the 3-step SUD regimen were similar to those in the iNHL expansion cohort using the 2-step SUD regimen. The response analysis for the pooled FL patients were consistent with the results for the iNHL expansion cohort.

FL cohort from the GCT3013-04 study

Further efficacy data of study GCT3013-04, which is a phase 1/2 , open-label, single-country, interventional trial in Japanese subjects with r/r B-NHL, were submitted as supportive data. As the date cutoff date of 21 April 2023, a total of 21 subjects were enrolled in the FL expansion cohort across 12 sites in Japan. All 21 subjects enrolled received at least 1 dose of epcoritamab. All subjects were of Asian race and Japanese ethnicity, further the study population in study GCT3013-04 was comparable to the FL patients included in study GCT3013-01.

The ORR (CR + PR) for subjects in the FL expansion cohort was 95.2% (95% CI: 76.2%, 99.9%), with 76.2% (16 subjects) and 19.0% (4 subjects) in subjects achieving best response of CR and PR, respectively. After a median DOR follow-up of 15.3 months (95% CI: 9.7, 20.6), the median DOR was 23.1 months (95% CI: 4.4, NR).

The results seem to be slightly better compared to the results of the pivotal study, however follow-up of the pivotal study was shorter, and the number of patients in the GCT3013-04 trial was limited and comparison across study has limitations.

Real world data/matching adjusted indirect comparisons (MAIC)

Real world study data of a total of 240 FL patients treated at any time from January 2010 through December 2022 using longitudinal data from the COTA electronic health records (EHR) database (COTA, New York, NY, USA), was also provided. The CR rate and ORR for all patients (third-line therapy or later) were 24.7% and 64.9%, respectively. Median (95% CI) DOR was 13.1 (12.0–16.2) months.

Interpretation of real world data in comparison of trial results is hampered by potential differences in between study population, differences in timing of efficacy assessments, and differences in response criteria. As time-to-event endpoints are not only confounded by potential differences at baseline but also by potential differences between study populations in e.g., clinical treatment decisions even when in response to similar post-baseline events these are not discussed here. Overall, no firm conclusion can be drawn from the provided real world data.

Finally, indirect comparisons of results from the epcoritamab trial vs comparator trial in the r/r FL after two or more systemic therapies (chemo-immunotherapy [CIT] (SCHOLAR-5), mosunetuzumab (GO29781, NCT02500407), tisagenlecleucel [tisa-cel] (ELARA, NCT03568461), and axicabtagene ciloleucel [axi-cel] (ZUMA-5, NCT03105336)) were submitted. A MAIC approach was used. After adjusting and matching the overlapping populations between GCT3013-01 and SCHOLAR-5, epcoritamab demonstrated significantly higher response rates than CIT: adjusted ORR (90.9% vs. 56.8%) and adjusted CR (73.7% vs. 32.0%) for epcoritamab vs. CIT, respectively.

The adjusted and matched populations between GCT3013-01 and GO29781, showed no significant difference in the response rates provided by epcoritamab vs. mosunetuzumab (adjusted ORR 84.3% vs. 80.0%, respectively). Similar, also no significant differences was seen for adjusted and matched population of GCT3013-01 and ELARA, response rates between epcoritamab vs tis-cell were comparable (adjusted ORR 85.5% vs. 86.2% respectively). The adjusted ORR for axicel (from the ZUMA-5 trial) was slightly higher than for epcoritamab (Adjusted ORR 93.7% vs. 86.2%, respectively).

Even though comparison analysis were conducted with overlapping and matched population, results from this indirect comparison should be interpretated with caution, as still differences may exist between studies that are not considered during the analysis but might impact the study results. No robust conclusions can be drawn from these analysis.

Additional efficacy data needed in the context of a conditional MA

Tepkinly was initially, and currently is, approved by a conditional marketing authorisation (CMA). As the underlying data supporting this new indication is regarded as not comprehensive, the MAH also requested a conditional marketing approval for this indication, i.e. the treatment of adult patients with R/R FL after two or more lines of systemic therapy. Epcoritamab was granted orphan medicinal product designation for the treatment of FL, that is still an incurable malignancy, and therefore falls under the scope of Article 2 (1) and (3) of the conditional marketing authorization (CMA) Regulation (EC) No. 507/2006. Importantly, this indication is supported by results of a single arm phase I/II study (GCT3013-01), with a dose escalation-expansion and optimization cohort and a single arm supportive study (GCT3013-04). The single arm study design of the pivotal study introduces uncertainties, for which confirmation of efficacy in the R/RFL population is needed to obtain a full approval.

In order to confirm the efficacy and safety of epcoritamab in the treatment of R/R FL after two or more lines of systemic therapy, the MAH will submit the final results, including efficacy and safety analyses, of the iNHL expansion cohort and FL optimization cohort of study GCT3013-01 will be submitted (RMP Category 2).

In order to confirm the efficacy of Tepkinly in adult patients with r/r FL, the MAH will submit the results of the ongoing Study M20-638 (A Phase 3, Open-Label Study to Evaluate Safety and Efficacy of Epcoritamab in Combination with Rituximab and Lenalidomide (R2) compared to R2 in Subjects with Relapsed or refractory Follicular Lymphoma (EPCORE™FL-1)) as the confirmatory study. Primary endpoint for the study is PFS and main secondary outcome measures are percentage of participants achieving CR, OS, and percentage of participants achieving MRD negativity.

2.4.4. Conclusions on the clinical efficacy

Clinically relevant ORR and CR were observed in the study population of FL R/R after two or more lines of systemic therapy. As these results are derived from a single arm trial phase 1/2 design confirmation of efficacy in the R/R FL population is required for a full approval.

The following measures are considered necessary to address issues related to clinical efficacy:

- In order to confirm the efficacy and safety of epcoritamab in the treatment of R/R FL after two or more lines of systemic therapy, the final CSRs, including efficacy and safety analyses, for the iNHL expansion cohort and FL optimization cohort of study GCT3013-01 will be submitted (RMP Category 2).
- In order to confirm the efficacy and safety of epcoritamab in the treatment of R/R FL after two or more lines of systemic therapy, the final CSRs, including efficacy and safety analyses, for study M20-638, a phase 3, open-label study of epcoritamab in combination with R2 compared to R2 in subjects with RR FL will be submitted in Q4/2030 (RMP Category 2).

2.5. Clinical safety

Introduction

The safety profile for epcoritamab was established in patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) treated with epcoritamab 0.16/0.8 mg/48 mg in GCT3013-01 study. Supportive data at the time of this MAA were 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). The most common adverse reactions (≥ 20%) were CRS, fatigue, neutropenia, injection site reactions, musculoskeletal pain, abdominal pain, pyrexia, nausea and diarrhoea. Serious adverse reactions occurred in 52% of patients. AESIs were CRS (any Grade: 51% Grade 3: 3.0%. CRS of any grade occurred in 6.6% of patients after the priming dose; 13% after the intermediate dose (Cycle 1, Day 8); 44% after the first full dose (Cycle 1, Day 15), 4.6% after the second full dose (Cycle 1 Day 22) and 2.8% after the third full dose (Cycle 2 Day 1) or beyond; ICANS occurred in 6.0% of the patients (one patient (0.6%) with Grade 5 ICANS); TLS occurred in 1.8% of patients (no severe cases were seen). Important identified risks associated with epcoritamab therapy are CRS, ICANS, and (serious) infections. The latter are observed in 25% of the patients including Grade 5 events in 4.2% of the patients. Risk of overdose due to medication errors is an important potential risk and long term safety data is missing information.

Safety studies and analysis sets

The Primary and Supportive Safety Analysis Sets used included subjects who were assigned to the 48 mg full dose and received at least 1 dose of epcoritamab, defined as the following:

- The Primary Safety Analysis Set (Safety Pool 01 R/R FL [N=129]) included all R/R FL subjects who were assigned to the 48 mg full dose and received at least 1 dose of epcoritamab in the Escalation or Expansion Parts of Study GCT3013-01.

Supportive Safety Analysis Sets:

- Safety Pool 01+04 R/R FL (N=151) included all R/R FL subjects who were assigned to the 48 mg full dose and received at least 1 dose of epcoritamab in the Escalation or Expansion Parts of Studies GCT3013-01 and GCT3013-04.
- Safety Pool 01+04 All B-NHL (N=449) included all B-NHL subjects who were assigned to the 48 mg full dose and received at least 1 dose of epcoritamab in the Escalation or Expansion Parts of Studies GCT3013-01 and GCT3013-04.

In addition to the Safety Analysis Sets defined above, initial data from 30 subjects with R/R FL who were assigned to the 3-step SUD regimen of epcoritamab 0.16/0.8/3/48 mg and have received at least 1 dose of study drug in the FL optimization cohort of Study GCT3013-01 are also provided. A data cutoff date of 21 April 2023 was used for safety.

Safety evaluations

Safety evaluations were based on the incidence and severity of treatment-emergent adverse events (TEAEs), deaths, serious TEAEs, discontinuations due to TEAEs, and dose delays due to TEAEs. A TEAE is defined as a newly occurring or worsening AE during the on-treatment period (treatment-emergent):

- Study GCT3013-01 Dose Escalation Part: from the day of first dose of study drug to 28 days after last dose of study drug, or initiation of new anti lymphoma therapy, whichever came first.
- Study GCT3013-01 Expansion Part + Study GCT3013-04 Dose Escalation and Expansion Parts: from the day of first dose of study drug to 60 days after last dose of study drug, or initiation of new anti-lymphoma therapy, whichever came first.

TEAEs were coded to standard preferred terms (PTs) and System Organ Classes (SOCs) using the Medical Dictionary for Regulatory Activities (MedDRA, v26.0 for all studies). TEAE severity was graded according to NCI CTCAE v5.0 except for the following: CRS events and ICANS events were graded using ASTCT criteria (Lee 2019) and CTLS according to Cairo-Bishop criteria (Coiffier 2008).CRS, ICANS, and CTLS were considered adverse events (AE) of special interest (AESIs) in Studies GCT3013-01 and GCT3013-04. CRS and ICANS were graded by American Society for Transplantation and Cellular Therapy (ASTCT) criteria (Lee 2019). Clinical tumour lysis syndrome (CTLS) was graded by Cairo-Bishop criteria (Coiffier 2008) (and not National Cancer Institute [NCI]-Common Terminology Criteria for Adverse Events [CTCAE]; hereinafter referred to as "CTCAE"). Note: All TEAEs of pyrexia during trial conduct were queried and confirmed by the investigator to be considered not attributed to CRS. If a fever (pyrexia) was a symptom of CRS, it was summarized as such and not as a separate AE. Other safety topics discussed include neurological events, serious infections, cytopenia events, pyrexia (not attributed to CRS), injection site reactions, systemic administration-related reactions, tumour flare, and hemophagocytic lymphohistiocytosis.

Patient exposure

In Safety Pool 01 R/R FL (N=129), the median duration of treatment was 8.3 months, and the median number of cycles of treatment initiated per subject was 8.0 cycles. A total of 75.2%, 59.7%, 45.7%, and 37.2% of subjects received at least 3 months, 6 months, 9 months, and 12 months of treatment, respectively. As of the data cutoff date of 21 April 2023, 47 (36.4%) subjects were still on treatment. Median relative dose intensity (RDI) was 98.6%, 100.0%, and 99.1% during the once every week (QW), once every 2 weeks (Q2W), and once every 4 weeks (Q4W) dosing schedules, respectively. Overall, 68.2% of subjects required a dose delay, including 58.9% of subjects due to an AE and 27.1% of subjects who required a dose delay for another reason, including COVID-19 control measures.

Fifteen (11.6%) subjects required epcoritamab re-priming. For these 15 subjects with FL, dose delays prior to re-priming were due to AEs in 13 subjects (7 related to COVID-19, COVID infection, and COVID-19 infection; 1 each related to polyneuropathy, cellulitis, cardiac insufficiency, paraneoplastic pemphigus, general weakness, and post-operative infection) and other reasons in 2 subjects (1 subject required additional assessment for lymphoma assessment and 1 subject required re-priming due to a scheduling issue). Fourteen of the 15 subjects did not experience a CRS event after re-priming.

In Safety Pool 01+04 R/R FL (N = 151), the median duration of treatment was 8.4 months (range: < 1, 30) and median number of cycles of treatment administered per subject was 9.0 (range < 1, 33). A total of 59 (39.1%) and 28 (18.5%) subjects received at least 12 months and 18 months of treatment, respectively. In Safety Pool 01+04 All B-NHL (N = 449), the median duration of treatment was 6.2 months (range: < 1, 34) and median number of cycles of treatment administered per subject was 7.0 (range 1, 35). A total of 144 (32.1%) and 86 (19.2%) subjects received at least 12 months and 18 months of treatment, respectively.

Exposure data from the Safety Pool 01+04 R/R FL (N=151) and Safety Pool 01+04 All B-NHL (N=449) were comparable to the primary Safety Pool 01 R/R FL, except for the treatment duration (median 8.3 months versus 6.2 months, respectively) and the number of dose delays (68.2% versus 55.5%) in the primary Safety Pool 01 R/R FL and the Safety Pool 01+04 All B-NHL).

Adverse events

An overview of TEAEs is given in Table 27.

Table 27: Overview of Treatment-Emergent Adverse Events in the GCT3013-01 study and safety pools

	GCT3013-01 ESC+EXP	**GCT3013-01 ESC+EXP and GCT3013-04 ESC+EXP**	
	R/R FL (N=129)	**R/R FL (N=151)**	**All B-NHL (N=449)**
Number of subjects with at least one TEAE	127 (98.4%)	149 (98.7%)	444 (98.9%)
Drug-related TEAE	120 (93.0%)	142 (94.0%)	406 (90.4%)
Grade 3 and higher TEAE	89 (69.0%)	105 (69.5%)	333 (74.2%)
Grade 3 and higher drug-related TEAE	48 (37.2%)	61 (40.4%)	206 (45.9%)
Grade 3 or 4 TEAE	84 (65.1%)	100 (66.2%)	321 (71.5%)
Grade 3 or 4 drug-related TEAE	48 (37.2%)	61 (40.4%)	202 (45.0%)
TEAE by worst toxicity grade			
1	7 (5.4%)	9 (6.0%)	24 (5.3%)
2	31 (24.0%)	35 (23.2%)	87 (19.4%)
3	51 (39.5%)	61 (40.4%)	174 (38.8%)
4	25 (19.4%)	31 (20.5%)	113 (25.2%)
5	13 (10.1%)	13 (8.6%)	46 (10.2%)[c]
Serious TEAE	89 (69.0%)	101 (66.9%)	300 (66.8%)
Serious drug-related TEAE	60 (46.5%)	71 (47.0%)	198 (44.1%)

	GCT3013-01 ESC+EXP	GCT3013-01 ESC+EXP and GCT3013-04 ESC+EXP	
	R/R FL (N=129)	R/R FL (N=151)	All B-NHL (N=449)
TEAE leading to treatment discontinuation	24 (18.6%)	28 (18.5%)	76 (16.9%)
Drug-related TEAE leading to treatment discontinuation	5 (3.9%)	7 (4.6%)	19 (4.2%)
TEAE leading to dose delay[a]	77 (59.7%)	87 (57.6%)	236 (52.6%)
Drug-related TEAE leading to dose delay[a]	45 (34.9%)	52 (34.4%)	136 (30.3%)
Fatal TEAE[b]	13 (10.1%)	13 (8.6%)	47 (10.5%)
Fatal drug-related TEAE	0	0	6 (1.3%)
AESIs			
CRS			
All grade	86 (66.7%)	105 (69.5%)	289 (64.4%)
Grade 3 and higher	2 (1.6%)	3 (2.0%)	25 (5.6%)
ICANS			
All grade	8 (6.2%)	8 (5.3%)	28 (6.2%)
Grade 3 and higher	0	0	3 (0.7%)
CTLS			
All grade	0	0	7 (1.6%)
Grade 3 and higher	0	0	4 (0.9%)

AESI = adverse event of special interest; B-NHL = B-cell non-Hodgkin lymphoma; COVID-19 = Coronavirus Disease-2019; CRS = cytokine release syndrome; CTLS = clinical tumour lysis syndrome; ESC = Escalation; EXP = Expansion; FL = follicular lymphoma; ICANS=immune effector cell-associated neurotoxicity syndrome; ISS = Integrated Summary of Safety; R/R = relapsed or refractory; TEAE = treatment-emergent adverse event
Note: Percentages calculated based on N.
Refer to ISS Table 3.0 for list of search criteria used for all AESIs and other safety topics of interest.
a. Includes TEAEs with action taken of dose delay or dose interruption.
b. Five of the subjects in the All B-NHL group reported in this row (0, 0 subjects in each column, respectively) are also reported by the investigator with primary cause of death as disease progression.
c. One additional event of COVID-19 pneumonia resulted in death but was inadvertently categorized as Grade 4 instead of Grade 5.
Source: ISS Table 3.1

In Safety Pool 01 R/R FL (N=129), 98.4% of subjects experienced at least 1 TEAE. TEAEs reported in ≥ 20% of subjects included CRS, injection site reaction, COVID-19, fatigue, diarrhea, pyrexia (not attributed to CRS), and neutropenia. The most common TEAEs are shown in Table 28. In Safety Pool 01 R/R FL (N=129), Grade 3 or 4 TEAEs were reported in 65.1% of subjects. The most frequently reported (≥ 10% of subjects) Grade 3 or 4 TEAEs included neutropenia and COVID-19 (Table 29).

In general, the patterns observed in common TEAEs were similar to those reported above for Safety Pool Safety Pool 01+04 R/R FL and All B-NHL. TEAEs in SOCs Infections and infestations (77.5% versus 64.4%), skin and subcutaneous tissues disorders (48.8% versus 37.6%), respiratory, thoracic and mediastinal disorders (43.4% versus 34.1%) were observed more frequently in Safety Pool 01 R/R FL patients compared to all B-NHL patients.

Table 28: Treatment-Emergent Adverse Events in ≥ 10% of Subjects in Any Group by SOC and PT

	GCT3013-01 ESC+EXP	GCT3013-01 ESC+EXP and GCT3013-04 ESC+EXP	
System Organ Class Preferred Term	**R/R FL (N=129)**	**R/R FL (N=151)**	**All B-NHL (N=449)**
Subjects with at least one TEAE	127 (98.4%)	149 (98.7%)	444 (98.9%)
General disorders and administration site conditions	101 (78.3%)	119 (78.8%)	332 (73.9%)
Injection site reaction	47 (36.4%)	63 (41.7%)	146 (32.5%)

System Organ Class Preferred Term	GCT3013-01 ESC+EXP R/R FL (N=129)	GCT3013-01 ESC+EXP and GCT3013-04 ESC+EXP R/R FL (N=151)	 All B-NHL (N=449)
Fatigue	39 (30.2%)	39 (25.8%)	107 (23.8%)
Pyrexia	32 (24.8%)	37 (24.5%)	100 (22.3%)
Injection site erythema	23 (17.8%)	24 (15.9%)	52 (11.6%)
Oedema peripheral	18 (14.0%)	19 (12.6%)	50 (11.1%)
Infections and infestations	100 (77.5%)	112 (74.2%)	289 (64.4%)
COVID-19	40 (31.0%)	43 (28.5%)	101 (22.5%)
Upper respiratory tract infection	17 (13.2%)	18 (11.9%)	33 (7.3%)
Urinary tract infection	13 (10.1%)	13 (8.6%)	34 (7.6%)
Immune system disorders	87 (67.4%)	106 (70.2%)	296 (65.9%)
Cytokine release syndrome	86 (66.7%)	105 (69.5%)	289 (64.4%)
Gastrointestinal disorders	79 (61.2%)	91 (60.3%)	272 (60.6%)
Diarrhoea	34 (26.4%)	36 (23.8%)	94 (20.9%)
Nausea	22 (17.1%)	24 (15.9%)	82 (18.3%)
Constipation	20 (15.5%)	25 (16.6%)	63 (14.0%)
Abdominal pain	12 (9.3%)	12 (7.9%)	46 (10.2%)
Vomiting	11 (8.5%)	12 (7.9%)	45 (10.0%)
Skin and subcutaneous tissue disorders	63 (48.8%)	79 (52.3%)	169 (37.6%)
Rash	11 (8.5%)	19 (12.6%)	44 (9.8%)
Nervous system disorders	61 (47.3%)	66 (43.7%)	172 (38.3%)
Headache	25 (19.4%)	26 (17.2%)	58 (12.9%)
Dizziness	15 (11.6%)	16 (10.6%)	34 (7.6%)
Blood and lymphatic system disorders	57 (44.2%)	60 (39.7%)	189 (42.1%)
Neutropenia	26 (20.2%)	27 (17.9%)	94 (20.9%)
Anaemia	19 (14.7%)	19 (12.6%)	78 (17.4%)
Thrombocytopenia	11 (8.5%)	11 (7.3%)	45 (10.0%)
Respiratory, thoracic and mediastinal disorders	56 (43.4%)	61 (40.4%)	153 (34.1%)
Cough	22 (17.1%)	25 (16.6%)	53 (11.8%)
Dyspnoea	18 (14.0%)	18 (11.9%)	41 (9.1%)
Investigations	53 (41.1%)	66 (43.7%)	205 (45.7%)
Neutrophil count decreased	13 (10.1%)	20 (13.2%)	58 (12.9%)
Musculoskeletal and connective tissue disorders	49 (38.0%)	58 (38.4%)	165 (36.7%)
Arthralgia	18 (14.0%)	19 (12.6%)	37 (8.2%)
Back pain	15 (11.6%)	19 (12.6%)	48 (10.7%)
Metabolism and nutrition disorders	45 (34.9%)	54 (35.8%)	182 (40.5%)
Decreased appetite	12 (9.3%)	14 (9.3%)	56 (12.5%)
Psychiatric disorders	28 (21.7%)	35 (23.2%)	91 (20.3%)
Insomnia	16 (12.4%)	21 (13.9%)	54 (12.0%)

B-NHL = B-cell non-Hodgkin lymphoma; COVID-19 = Coronavirus-Disease-2019; ESC = Escalation; EXP = Expansion; FL = follicular lymphoma; ISS = Integrated Summary of Safety; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; R/R = relapsed or refractory; SOC = System Organ Class; TEAE = treatment-emergent adverse event; v = version.
Note: Percentages calculated based on N.
Adverse events are classified using MedDRA v26.0 and are counted only once per system organ class and only once per preferred term.
Source: ISS Table 3.3

Table 29: Grade 3 or 4 TEAEs in ≥ 3% of Subjects in Any Group by SOC and PT

	GCT3013-01 ESC+EXP	GCT3013-01 ESC+EXP and GCT3013-04 ESC+EXP	
System Organ Class Preferred Term	**R/R FL (N=129)**	**R/R FL (N=151)**	**All B-NHL (N=449)**
Subjects with at least one Grade 3 or 4 TEAE	84 (65.1%)	100 (66.2%)	321 (71.5%)
Infections and infestations	43 (33.3%)	49 (32.5%)	131 (29.2%)
COVID-19	14 (10.9%)	15 (9.9%)	36 (8.0%)
Pneumonia	6 (4.7%)	7 (4.6%)	18 (4.0%)
Urinary tract infection	5 (3.9%)	5 (3.3%)	10 (2.2%)
COVID-19 pneumonia	4 (3.1%)	5 (3.3%)	16 (3.6%)
Blood and lymphatic system disorders	40 (31.0%)	42 (27.8%)	140 (31.2%)
Neutropenia	22 (17.1%)	23 (15.2%)	77 (17.1%)
Anaemia	8 (6.2%)	8 (5.3%)	45 (10.0%)
Lymphopenia	8 (6.2%)	8 (5.3%)	21 (4.7%)
Thrombocytopenia	5 (3.9%)	5 (3.3%)	26 (5.8%)
Febrile neutropenia	4 (3.1%)	5 (3.3%)	11 (2.4%)
Investigations	24 (18.6%)	33 (21.9%)	107 (23.8%)
Neutrophil count decreased	12 (9.3%)	17 (11.3%)	52 (11.6%)
Lymphocyte count decreased	6 (4.7%)	9 (6.0%)	28 (6.2%)
Alanine aminotransferase increased	3 (2.3%)	7 (4.6%)	9 (2.0%)
Platelet count decreased	2 (1.6%)	2 (1.3%)	21 (4.7%)
Metabolism and nutrition disorders	10 (7.8%)	12 (7.9%)	48 (10.7%)
Type 2 diabetes mellitus	4 (3.1%)	4 (2.6%)	5 (1.1%)
Respiratory, thoracic and mediastinal disorders	8 (6.2%)	8 (5.3%)	29 (6.5%)
Pulmonary embolism	5 (3.9%)	5 (3.3%)	7 (1.6%)
Immune system disorders	3 (2.3%)	4 (2.6%)	26 (5.8%)
Cytokine release syndrome	2 (1.6%)	3 (2.0%)	23 (5.1%)

B-NHL = B-cell non-Hodgkin lymphoma; COVID-19 = Coronavirus-Disease-2019; ESC = Escalation; EXP = Expansion; FL = follicular lymphoma; ISS = Integrated Summary of Safety; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; R/R = relapsed or refractory; SOC = System Organ Class; TEAE = treatment-emergent adverse event; v = version.
Note: Percentages calculated based on N.
Adverse events are classified using MedDRA v26.0 and are counted only once per system organ class and only once per preferred term.

In Safety Pool 01 R/R FL (N=129), 93.0% of subjects experienced at least one TEAE considered drug related by the investigator, including 37.2% of subjects who had at least one Grade 3 or 4 drug-related TEAE. The most frequently reported (in ≥ 10% of subjects) treatment-related TEAEs included CRS, injection site reaction, fatigue, neutropenia, injection site erythema, pyrexia, and diarrhea (Table 30). The most frequently reported Grade 3 or 4 drug-related TEAEs (in ≥ 5% of the patients) were neutropenia (15.5%) and neutrophil count decreased (7.0%).

Table 30: Treatment-Related TEAEs in ≥ 5% of Subjects in Any Group by SOC and PT

	GCT3013-01 ESC+EXP	GCT3013-01 ESC+EXP and GCT3013-04 ESC+EXP	
System Organ Class Preferred Term	**R/R FL (N=129)**	**R/R FL (N=151)**	**All B-NHL (N=449)**
Subjects with at least one drug-related TEAE	120 (93.0%)	142 (94.0%)	406 (90.4%)
General disorders and administration site conditions	88 (68.2%)	105 (69.5%)	260 (57.9%)
Injection site reaction	47 (36.4%)	63 (41.7%)	146 (32.5%)

System Organ Class Preferred Term	GCT3013-01 ESC+EXP R/R FL (N=129)	GCT3013-01 ESC+EXP and GCT3013-04 ESC+EXP R/R FL (N=151)	 All B-NHL (N=449)
Fatigue	24 (18.6%)	24 (15.9%)	63 (14.0%)
Injection site erythema	22 (17.1%)	23 (15.2%)	51 (11.4%)
Pyrexia	16 (12.4%)	17 (11.3%)	45 (10.0%)
Injection site rash	10 (7.8%)	10 (6.6%)	19 (4.2%)
Chills	8 (6.2%)	8 (5.3%)	16 (3.6%)
Immune system disorders	87 (67.4%)	106 (70.2%)	293 (65.3%)
Cytokine release syndrome	86 (66.7%)	105 (69.5%)	289 (64.4%)
Blood and lymphatic system disorders	40 (31.0%)	42 (27.8%)	132 (29.4%)
Neutropenia	24 (18.6%)	25 (16.6%)	77 (17.1%)
Anaemia	8 (6.2%)	8 (5.3%)	29 (6.5%)
Thrombocytopenia	7 (5.4%)	7 (4.6%)	23 (5.1%)
Skin and subcutaneous tissue disorders	33 (25.6%)	45 (29.8%)	88 (19.6%)
Dry skin	7 (5.4%)	8 (5.3%)	10 (2.2%)
Rash	4 (3.1%)	10 (6.6%)	25 (5.6%)
Gastrointestinal disorders	31 (24.0%)	34 (22.5%)	88 (19.6%)
Diarrhoea	14 (10.9%)	15 (9.9%)	31 (6.9%)
Nausea	8 (6.2%)	9 (6.0%)	29 (6.5%)
Investigations	30 (23.3%)	41 (27.2%)	121 (26.9%)
Neutrophil count decreased	10 (7.8%)	16 (10.6%)	47 (10.5%)
Alanine aminotransferase increased	4 (3.1%)	9 (6.0%)	21 (4.7%)
Aspartate aminotransferase increased	3 (2.3%)	8 (5.3%)	18 (4.0%)
Platelet count decreased	3 (2.3%)	3 (2.0%)	25 (5.6%)
Nervous system disorders	26 (20.2%)	29 (19.2%)	71 (15.8%)
Headache	10 (7.8%)	10 (6.6%)	21 (4.7%)
Immune effector cell-associated neurotoxicity syndrome	8 (6.2%)	8 (5.3%)	28 (6.2%)
Metabolism and nutrition disorders	15 (11.6%)	19 (12.6%)	63 (14.0%)
Decreased appetite	6 (4.7%)	7 (4.6%)	23 (5.1%)

B-NHL = B-cell non-Hodgkin lymphoma; ESC = Escalation; EXP = Expansion; FL = follicular lymphoma; ISS = Integrated Summary of Safety; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; R/R = relapsed or refractory; SOC = System Organ Class; TEAE = treatment-emergent adverse event; v = version.
Note: Percentages calculated based on N.
Adverse events are classified using MedDRA v26.0 and are counted only once per system organ class and only once per preferred term.
Source: ISS Table 3.7

Serious adverse event/deaths/other significant events

Serious adverse events

In Safety Pool 01 R/R FL (N=129), serious TEAEs were reported for 69.0% of subjects. The most frequently reported (in ≥ 5% of subjects) serious TEAEs included CRS (41.9%), COVID-19 (11.6%), COVID-19 pneumonia (7.8%), and pneumonia (5.4%; Table 31). Overall, 46.5% of subjects experienced serious TEAEs that were considered related to study drug by the investigator, with the most frequently reported drug-related serious TEAEs (≥ 2% of subjects) being CRS (41.9%) and COVID-19, ICANS, and pneumonia (2.3% each).

Table 31: Serious TEAEs Reported in ≥ 2% of Subjects in Any Group by SOC and PT

	GCT3013-01 ESC+EXP	GCT3013-01 ESC+EXP and GCT3013-04 ESC+EXP	
System Organ Class Preferred Term	**R/R FL (N=129)**	**R/R FL (N=151)**	**All B-NHL (N=449)**
Subjects with at least one serious TEAE	89 (69.0%)	101 (66.9%)	300 (66.8%)
Immune system disorders	54 (41.9%)	59 (39.1%)	161 (35.9%)
Cytokine release syndrome	54 (41.9%)	59 (39.1%)	161 (35.9%)
Infections and infestations	52 (40.3%)	60 (39.7%)	156 (34.7%)
COVID-19	15 (11.6%)	16 (10.6%)	40 (8.9%)
COVID-19 pneumonia	10 (7.8%)	11 (7.3%)	33 (7.3%)
Pneumonia	7 (5.4%)	8 (5.3%)	21 (4.7%)
Pneumocystis jirovecii pneumonia	3 (2.3%)	3 (2.0%)	4 (0.9%)
Herpes zoster	1 (0.8%)	3 (2.0%)	6 (1.3%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	10 (7.8%)	13 (8.6%)	34 (7.6%)
Bowen's disease	2 (1.6%)	3 (2.0%)	4 (0.9%)
General disorders and administration site conditions	9 (7.0%)	9 (6.0%)	28 (6.2%)
Pyrexia	5 (3.9%)	5 (3.3%)	13 (2.9%)
Nervous system disorders	8 (6.2%)	9 (6.0%)	28 (6.2%)
Immune effector cell-associated neurotoxicity syndrome	3 (2.3%)	3 (2.0%)	13 (2.9%)
Metabolism and nutrition disorders	6 (4.7%)	6 (4.0%)	11 (2.4%)
Type 2 diabetes mellitus	4 (3.1%)	4 (2.6%)	4 (0.9%)
Respiratory, thoracic and mediastinal disorders	5 (3.9%)	5 (3.3%)	24 (5.3%)
Pleural effusion	1 (0.8%)	1 (0.7%)	10 (2.2%)
Blood and lymphatic system disorders	4 (3.1%)	4 (2.6%)	14 (3.1%)
Febrile neutropenia	3 (2.3%)	3 (2.0%)	8 (1.8%)

B-NHL = B-cell non-Hodgkin lymphoma; COVID-19 = Coronavirus-Disease-2019; ESC = Escalation; EXP = Expansion; FL = follicular lymphoma; ISS = Integrated Summary of Safety; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; R/R = relapsed or refractory; SOC = System Organ Class; TEAE = treatment-emergent adverse event; v = version.
Note: Percentages calculated based on N.
Adverse events are classified using MedDRA v26.0 and are counted only once per system organ class and only once per preferred term.
Source: ISS Table 3.14

Deaths

In Safety Pool 01 R/R FL (N=129), a total of 34 (26.4%) subjects died during the study as of the data cutoff date, including 14 (10.9%) subjects who died on-treatment (i.e., within 60 days of the last dose of epcoritamab) and 20 subjects who died during the survival follow-up period (i.e., > 60 days after the last dose of epcoritamab. See Table 32.

Of the 15 deaths due to AE during the study, 11 occurred on-treatment (within 60 days of the last dose of epcoritamab; Table 32) and 4 occurred during the survival follow-up period (> 60 days post last dose) One of the 4 deaths during the survival follow-up period occurred in a subject who had a nonfatal treatment-related TEAE of multisystem inflammatory syndrome in adults that resolved and then had a recurrent multisystem inflammatory syndrome beyond 60 days post last dose (and thus nontreatment-emergent) that was considered treatment related and resulted in death during the survival follow-up period.

A total of 13 (10.1%) subjects experienced fatal TEAEs (Table 33). According to the MAH there is an apparent discrepancy between the 11 subjects who died on-treatment (i.e., within 60 days of the last dose of epcoritamab) and the 13 subjects in who experienced fatal TEAEs. This is because there were 3

subjects whose TEAEs with fatal outcome started during the treatment-emergent period but were long in duration such that the resulting death occurred beyond 60 days after the last dose of epcoritamab (i.e., during the survival follow-up period), and another subject whose fatal AE (sepsis) occurred within 60 days of last epcoritamab dose but after initiation of new anti-lymphoma therapy (i.e., conditioning chemotherapy/allogenic stem cell transplant), rendering it non treatment-emergent. The only fatal TEAE reported in more than 1 (0.8%) subject was COVID-19 pneumonia (5 subjects, 3.9%).

Two fatal TEAEs included events of lymphoma transformation and myelodysplastic syndrome (MDS) (1 subject each). The event of lymphoma transformation was due to underlying disease progression. The event of MDS was a pre-existing condition that was diagnosed 7 days after enrolment; the subject discontinued treatment due to worsening of MDS and later died due to progression of MDS. No fatal TEAE in the Safety Pool 01 R/R FL was considered related to the study drug by the investigator.

Table 32: Summary of Deaths

	GCT3013-01 ESC+EXP	**GCT3013-01 ESC+EXP and GCT3013-04 ESC+EXP**	
	R/R FL (N=129)	**R/R FL (N=151)**	**All B-NHL (N=449)**
Deaths	34 (26.4%)[a]	35 (23.2%)[b]	186 (41.4%)[c]
Primary cause of death			
Disease progression	12 (9.3%)	12 (7.9%)	117 (26.1%)
Adverse event	15 (11.6%)	15 (9.9%)	45 (10.0%)
Other[d]	7 (5.4%)	8 (5.3%)	21 (4.7%)
Unknown	0	0	3 (0.7%)
Deaths within 60 days of first dose	3 (2.3%)	3 (2.0%)	43 (9.6%)
Primary cause of death			
Disease progression	1 (0.8%)	1 (0.7%)	30 (6.7%)
Adverse event	2 (1.6%)	2 (1.3%)	13 (2.9%)
Deaths within 60 days of last dose	14 (10.9%)	14 (9.3%)	79 (17.6%)
Primary cause of death			
Disease progression	3 (2.3%)	3 (2.0%)	50 (11.1%)
Adverse event	11 (8.5%)[e]	11 (7.3%)	28 (6.2%)
Other	0	0	1 (0.2%)

AE = adverse event; B-NHL = B-cell non-Hodgkin lymphoma; COVID-19 = Coronavirus Disease-2019; CSR = clinical study report; ESC = Escalation; EXP = Expansion; FL = follicular lymphoma; ISS = Integrated Summary of Safety; PT = preferred term; TEAE = treatment-emergent adverse event; R/R = relapsed or refractory.

a. Of the 34 deaths reported for Safety Pool 01 R/R FL, 20 deaths were reported during the survival follow-up period (> 60 days post last dose).

b. Of the 35 deaths reported for Safety Pool 01+04 R/R FL, 21 deaths were reported during the survival follow-up period (> 60 days post last dose).

c. Of the 186 deaths reported for Safety Pool 01+04 All B-NHL Pool, 107 deaths were reported during the survival follow-up period (> 60 days post last dose).

d. For additional details on what was included under "other," please see individual CSRs.

e. Note that 3 of the 13 FL subjects with fatal TEAEs in are not counted here, because the AEs with fatal outcome (PTs of organising pneumonia, COVID-19, and COVID-19 pneumonia) were long in duration that began during the treatment-emergent period (i.e., within 60 days of last epcoritamab dose), but the resulting death did not occur until beyond 60 days after the last dose of epcoritamab. In addition, there was a subject whose fatal AE (sepsis) occurred within 60 days of last epcoritamab dose (and thus captured here) but occurred after initiation of new anti-lymphoma therapy (i.e., conditioning chemotherapy/allogenic stem cell transplant), rendering it non-treatment-emergent.

Note: Percentages calculated based on N.
Source: ISS Table 3.35

Table 33: Fatal Treatment-Emergent Adverse Events by SOC and PT

	GCT3013-01 ESC+EXP	**GCT3013-01 ESC+EXP and GCT3013-04 ESC+EXP**	
System Organ Class Preferred Term	**R/R FL (N=129)**	**R/R FL (N=151)**	**All B-NHL (N=449)**
Subjects with at least one fatal TEAE	13 (10.1%)	13 (8.6%)	47 (10.5%)
Infections and infestations	8 (6.2%)	8 (5.3%)	31 (6.9%)

System Organ Class Preferred Term	GCT3013-01 ESC+EXP R/R FL (N=129)	GCT3013-01 ESC+EXP and GCT3013-04 ESC+EXP R/R FL (N=151)	 All B-NHL (N=449)
COVID-19 pneumonia	5 (3.9%)	5 (3.3%)	17 (3.8%)
COVID-19	1 (0.8%)	1 (0.7%)	6 (1.3%)
Pneumonia	1 (0.8%)	1 (0.7%)	2 (0.4%)
Pseudomonal sepsis	1 (0.8%)	1 (0.7%)	1 (0.2%)
Necrotising fasciitis	0	0	1 (0.2%)
Pneumonia bacterial	0	0	1 (0.2%)
Progressive multifocal leukoencephalopathy	0	0	1 (0.2%)
Septic shock	0	0	2 (0.4%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (1.6%)	2 (1.3%)	4 (0.9%)
Lymphoma transformation	1 (0.8%)	1 (0.7%)	1 (0.2%)
Myelodysplastic syndrome	1 (0.8%)	1 (0.7%)	1 (0.2%)
Malignant neoplasm progression	0	0	1 (0.2%)
Oncologic complication	0	0	1 (0.2%)
Respiratory, thoracic and mediastinal disorders	2 (1.6%)	2 (1.3%)	3 (0.7%)
Interstitial lung disease	1 (0.8%)	1 (0.7%)	1 (0.2%)
Organising pneumonia	1 (0.8%)	1 (0.7%)	1 (0.2%)
Pulmonary embolism	0	0	1 (0.2%)
Cardiac disorders	1 (0.8%)	1 (0.7%)	3 (0.7%)
Cardiopulmonary failure	1 (0.8%)	1 (0.7%)	1 (0.2%)
Myocardial infarction	0	0	1 (0.2%)
Myocarditis	0	0	1 (0.2%)
General disorders and administration site conditions	0	0	2 (0.4%)
General physical health deterioration	0	0	2 (0.4%)
Hepatobiliary disorders	0	0	1 (0.2%)
Hepatotoxicity	0	0	1 (0.2%)
Immune system disorders	0	0	2 (0.4%)
Cytokine release syndrome	0	0	2 (0.4%)
Nervous system disorders	0	0	2 (0.4%)
Immune effector cell-associated neurotoxicity syndrome	0	0	2 (0.4%)

B-NHL = B-cell non-Hodgkin lymphoma; COVID-19 = Coronavirus-Disease-2019; ESC = Escalation; EXP = Expansion; FL = follicular lymphoma; ISS = Integrated Summary of Safety; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; R/R = relapsed or refractory; SOC = System Organ Class; TEAE = treatment-emergent adverse event; v = version.
Note: Percentages calculated based on N.
Adverse events are classified using MedDRA v26.0 and are counted only once per system organ class and only once per preferred term.
Source: ISS Table 3.25

In the Safety Pool 01+04 All B-NHL fatal TEAEs (in non-FL subjects) reported in more than 1% of subjects included COVID-19 (6 subjects, 1.3%). Six (1.3%) subjects experienced drug-related fatal TEAEs, including 2 (0.4%) subjects each with CRS and ICANS and 1 (0.2%) subject each with COVID-19 pneumonia and pneumonia bacterial.

AESIs

CRS

The AESI of CRS was analyzed and summarized at the subject level (Table 34 and Table 35) and at the event level (see below). 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. Systemic

corticosteroids were administered as prophylaxis for CRS. All subjects in Safety Pool 01 R/R FL and Safety Pool 01+04 R/R FL and 99.8% of subjects in Safety Pool 01+04 All B-NHL received at least 1 prophylactic medication for CRS. In the Safety Pool 01 R/R FL, 15 (17.4%) subjects had CRS that led to dose delay. No subjects experienced CRS that led to treatment discontinuation. The median time to first CRS onset from first dose was 16.0 days, following administration of the first full dose of 48 mg epcoritamab on C1D15. All CRS events were resolved, with a median time to resolution of 2.0 days.

Table 34: Subject-Level Treatment-Emergent CRS Summary

	GCT3013-01 ESC+EXP	**GCT3013-01 ESC+EXP and GCT3013-04 ESC+EXP**	
	R/R FL (N=129)	**R/R FL (N=151)**	**All B-NHL (N=449)**
Subjects with at least one CRS event	86 (66.7%)	105 (69.5%)	289 (64.4%)
Grade 1	52 (40.3%)	66 (43.7%)	167 (37.2%)
Grade 2	32 (24.8%)	36 (23.8%)	97 (21.6%)
Grade 3	2 (1.6%)	3 (2.0%)	21 (4.7%)
Grade 4	0	0	2 (0.4%)
Grade 5	0	0	2 (0.4%)
Occurrence of any CRS signs and symptoms[a]	86 (100%)	105 (100%)	289 (100%)
Fever	86 (100%)	105 (100%)	288 (99.7%)
Hypotension	29 (33.7%)	33 (31.4%)	102 (35.3%)
Hypoxia	12 (14.0%)	14 (13.3%)	53 (18.3%)
Other[d]	37 (43.0%)	39 (37.1%)	84 (29.1%)
Subject with CRS[a]			
Treated with anti-cytokine therapy	31 (36.0%)	37 (35.2%)	112 (38.8%)
Tocilizumab	31 (36.0%)	37 (35.2%)	109 (37.7%)
Other anti-cytokine	0	0	1 (0.3%)
Treated with corticosteroid for CRS	17 (19.8%)	25 (23.8%)	74 (25.6%)
Treated with oxygen therapy	16 (18.6%)	18 (17.1%)	57 (19.7%)
Treated with vasopressor medication (excluding midodrine/midodrine hydrochloride, milrinone, vasopressin)	2 (2.3%)	2 (1.9%)	23 (8.0%)
Treated with vasopressin	0	0	3 (1.0%)
Leading to dose delay/interruption	15 (17.4%)	18 (17.1%)	41 (14.2%)
Leading to treatment discontinuation	0	0	4 (1.4%)
Time to first CRS onset from first dose (days)			
n	86	105	289
Median	16.0	16.0	16.0
Min, max	1, 56	1, 56	1, 73
Time to CRS resolution (days)[b,c]			
Subjects with resolved CRS[a]	86 (100%)	105 (100%)	284 (98.3%)
Median	2.0	3.0	3.0
Min, max	1, 54	1, 54	1, 54

ALT = alanine aminotransferase; AST = aspartate aminotransferase; ASTCT = American Society for Transplantation and Cellular Therapy; B-NHL = B-cell non-Hodgkin lymphoma; CRS = cytokine release syndrome; ESC = Escalation; EXP = Expansion; FL = follicular lymphoma; ISS = Integrated Summary of Safety; max = maximum; min = minimum; R/R = relapsed or refractory

a. Percentage calculated based on subjects with at least 1 CRS event.

b. Based on longest recorded CRS duration in subjects with >1 CRS event.

c. For subjects with multiple events, all events must be resolved.

d. Other includes headache, chills, tachycardia, nausea, vomiting, fatigue, diarrhoea, dizziness, blood creatinine increased, hypertransaminasaemia, malaise, night sweats, rash, sinus tachycardia, abdominal pain, abdominal pain upper, ALT increased, back pain, chest pain, dyspnoea, hypophosphataemia, myalgia, noncardiac chest pain, oliguria, pain, polyuria, pyrexia, rash erythematous, rash macular, rash maculo-papular, rash pruritic, somnolence, tachypnoea, tremor, urinary incontinence, arthralgia, AST increased, asthenia, ataxia, atrial fibrillation, C-reactive protein increased, confusional state, fall, hyperhidrosis, leukocytosis, muscular weakness, paraesthesia, pulmonary oedema, and vasoplegia syndrome.

Note: CRS events are graded according to ASTCT criteria (Lee 2019). The toxicity grade refers to the worst toxicity grade per subject.

Refer to ISS Table 3.0 for list of search criteria used for CRS.

Source: ISS Table 5.3

In Safety Pool 01+04 All B-NHL two (0.4%) subjects with MCL experienced Grade 4 CRS and 2 (0.4%) subjects experienced Grade 5 CRS (1 with MCL and 1 with other subtypes of iNHL), all of which occurred around the first full dose on C1D15. Four (1.4%) subjects experienced CRS leading to treatment discontinuation, including both Grade 5 CRS, 1 Grade 4 event in a subject with MCL, and 1 Grade 1 CRS in a subject with DLBCL. CRS events were not resolved for 5 subjects from Study GCT3013-01 who died. The 5 subjects included 1 subject with other subtypes of iNHL (Grade 5), 1 subject with MCL (Grade 5), 1 subject with MCL (Grade 4) who died on D47 due to disease progression, and 1 subject with DLBCL (Grade 3) who died on D46 due to disease progression, and 1 subject with DLBCL (Grade 2) who died on D34 due to disease progression.

Table 35: Subject-Level Treatment-Emergent CRS Summary by Dosing Period

Subgroup: GCT3013-01 ESC+EXP R/R FL	**Priming (N=129)**	**Intermediate (N=128)**	**First Full (N=127)**	**Second Full (N=125)**	**Third Full and after (N=125)**
Subjects with at least one CRS event	18 (14.0%)	16 (12.5%)	76 (59.8%)	11 (8.8%)	6 (4.8%)
Grade 1	12 (9.3%)	12 (9.4%)	49 (38.6%)	9 (7.2%)	5 (4.0%)
Grade 2	5 (3.9%)	4 (3.1%)	26 (20.5%)	2 (1.6%)	1 (0.8%)
Grade 3	1 (0.8%)	0	1 (0.8%)	0	0
Grade 4	0	0	0	0	0
Grade 5	0	0	0	0	0
Occurrence of any CRS signs and symptoms[a]	18 (100%)	16 (100%)	76 (100%)	11 (100%)	6 (100%)
Fever	17 (94.4%)	16 (100%)	76 (100%)	11 (100%)	6 (100%)
Hypotension	4 (22.2%)	4 (25.0%)	23 (30.3%)	1 (9.1%)	1 (16.7%)
Hypoxia	4 (22.2%)	0	8 (10.5%)	1 (9.1%)	1 (16.7%)
Other[e]	4 (22.2%)	4 (25.0%)	29 (38.2%)	3 (27.3%)	2 (33.3%)
Subject with CRS[a]					
Treated with anti-cytokine therapy	5 (27.8%)	2 (12.5%)	23 (30.3%)	2 (18.2%)	1 (16.7%)
Tocilizumab	5 (27.8%)	2 (12.5%)	23 (30.3%)	2 (18.2%)	1 (16.7%)
Treated with corticosteroid for CRS	2 (11.1%)	3 (18.8%)	10 (13.2%)	4 (36.4%)	0
Treated with oxygen therapy	4 (22.2%)	2 (12.5%)	11 (14.5%)	2 (18.2%)	1 (16.7%)
Treated with vasopressor medication (excluding midodrine/midodrine hydrochloride, milrinone, vasopressin)	1 (5.6%)	0	1 (1.3%)	0	0
Leading to dose delay/interruption	1 (5.6%)	1 (6.3%)	9 (11.8%)	2 (18.2%)	3 (50.0%)
Leading to treatment discontinuation	0	0	0	0	0
Time from most recent dosing (hours)[c]					
n	18	16	76	11	6
Median	15.6	22.3	15.3	61.0	10.7

Subgroup: GCT3013-01 ESC+EXP R/R FL	Priming (N=129)	Intermediate (N=128)	First Full (N=127)	Second Full (N=125)	Third Full and after (N=125)
Min, max	4, 165	6, 157	1, 130	9, 128	<1, 163
Time to CRS resolution (hours)[b,d]					
Subjects with resolved CRS[a]	18 (100%)	16 (100%)	76 (100%)	11 (100%)	6 (100%)
Median	10.3	21.1	38.5	28.2	84.2
Min, max	2, 52	2, 336	1, 216	2, 1296	24, 456

ALT = alanine aminotransferase; ASTCT = American Society for Transplantation and Cellular Therapy; CRS = cytokine release syndrome; ESC = Escalation; EXP = Expansion; FL = follicular lymphoma; ISS = Integrated Summary of Safety; max = maximum; min = minimum; R/R = relapsed or refractory

a. Percentage calculated based on subjects with at least 1 CRS event within the dosing period.
b. Based on longest recorded CRS duration in subjects with > 1 CRS event within the dosing period.
c. Based on the first CRS in subjects with > 1 CRS event within the dosing period.
d. For subjects with multiple events, all events must be resolved.
e. Other includes chills, vomiting, abdominal pain, headache, nausea, tachycardia, abdominal pain upper, ALT increased, back pain, blood creatinine increased, chest pain, diarrhoea, dizziness, dyspnoea, fatigue, hypertransaminasaemia, malaise, myalgia, night sweats, noncardiac chest pain, oliguria, pain, polyuria, pyrexia, rash, rash erythematous, rash macular, rash maculo-papular, rash pruritic, sinus tachycardia, somnolence, tachypnoea, tremor, and urinary incontinence.

Note: CRS events are graded according to ASTCT criteria (Lee 2019). The toxicity grade refers to the worst toxicity grade per subject.
Refer to ISS Table 3.0 for list of search criteria used for CRS.
Percentages are based on number of treated subjects in the analysis period.
If CRS time is completely missing, time to CRS onset will be imputed as minimum of 12 hours and time to T23:59 if CRS onset date fall 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. If CRS time contains hour part, but missing minute part, the minute part will be imputed as 00. For CRS resolution time, CRS onset and resolution time would be imputed as T00:00 and T23:59 if time component is missing.
Source: ISS Table 5.4

CRS per event level: in Safety Pool 01 R/R FL (N=129), a total of 143 CRS events were reported in 86 subjects, all were related to the study drug. Among these subjects, 61.6% of subjects had 1 CRS episode, 19.8% of subjects had 2 CRS episodes, 11.6% of subjects had 3 CRS episodes, 5.8% of subjects had 4 CRS episodes, and 1.2% of subjects had 6 CRS episodes. Most CRS events were Grade 1 (69.9%) or Grade 2 (28.7%) in severity. Two (1.4%) CRS events were Grade 3. There were no Grade 4 or 5 CRS events.

Tocilizumab use: In Safety Pool 01 R/R FL (N=129), a total of 143 CRS events of any grade were reported, and 35 (24.5%) of these events were managed with tocilizumab treatment. Among the 35 CRS events where tocilizumab was administered, 9 were Grade 1, 24 were Grade 2, and 2 were Grade 3.

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 initiated, AND
- The prophylactic corticosteroid dose as per protocol not escalated.

Among the 35 CRS events with tocilizumab administration, the majority (28 events, 80%) responded to tocilizumab. The tocilizumab response rate was 77.8%, 83.3%, and 50.0% for CRS of Grade 1, 2, and 3, respectively. There were 7 (20.0%) CRS events with tocilizumab administration that did not meet the response criteria above and were defined as tocilizumab "failures". The reasons for tocilizumab "failure" included the following; not resolved within 4 days following tocilizumab (4 events, 11.4%); new corticosteroids initiated (4 events, 11.4%); and prophylactic corticosteroids dose escalated (1 event, 2.9%). In Safety Pool 01+04 All B-NHL, 132/487 CRS events were treated with tocilizumab.

In addition to tocilizumab (discussed above) and corticosteroids, other most commonly used (in ≥ 10% of subjects) concomitant medications for CRS management in Safety Pool 01 R/R FL included paracetamol (79.1%), sodium chloride (27.9%), piperacillin sodium; tazobactam sodium (19.8%), oxygen (18.6%), and solutions affecting electrolyte balance (10.5%). The most commonly used concomitant medications for CRS management in Safety Pool 01+04 R/R FL and Safety Pool 01+04 All B-NHL were similar to that reported in Safety Pool 01 R/R FL.

ICANS

In Safety Pool 01 R/R FL (N=129), 8 (6.2%) subjects experienced ICANS. In 6 subjects, the ICANS overlapped with CRS events. The median time to first ICANS onset was 21.5 days from first dose and 3.5 days from the most recent dose of epcoritamab. All the events were considered treatment-related, and were Grade 1 (3.9%, 5 subjects) or Grade 2 (2.3%, 3 subjects) in severity. There were no Grade 3, 4, or 5 ICANS events in this population. ICANS led to dose delay in 1 (12.5%) subject. No ICANS led to treatment discontinuation. All ICANS events had resolved by the data cutoff date, with the median time to ICANS resolution being 2.0 days.

In Safety Pool 01+04 All B-NHL 28 (6.2%) subjects experienced ICANS. One (0.2%) subject experienced Grade 4 ICANS and 2 (0.4%) subjects experienced Grade 5 ICANS (compared with 0 subjects for both grades in Safety Pool 01 R/R FL). ICANS led to higher rates of dose delay (6 subjects, 21.4%) and treatment discontinuation (2 subjects, 7.1%) compared with 12.5% and 0, respectively, in Safety Pool 01 R/R FL. Three subjects had ICANS events that had not resolved, including 1 aNHL subject and 1 MCL subject with Grade 5 ICANS, and 1 MCL subject with Grade 2 ICANS that was resolving, but the subject died due to disease progression (compared with 0 unresolved ICANS events in Safety Pool 01 R/R FL).

In both Safety Pool 01 R/R FL and Safety Pool 01+04 R/R FL, 4 (50%) subjects who experienced ICANS were treated with at least 1 concomitant medication, including piperacillin sodium;tazobactam sodium (in 2 subjects) and amoxicillin;clavulanic acid, dexamethasone, prednisolone, levetiracetam, dimetindene maleate, sodium chloride, and famotidine (1 subject each). In Safety Pool 01+04 All B-NHL, 20 (71.4%) subjects who experienced ICANS were treated with at least 1 concomitant medication. The most commonly used (in ≥ 10% of subjects) concomitant medications for ICANS were dexamethasone (42.9%), levetiracetam (17.9%), tocilizumab (14.3%), and sodium chloride (10.7%).

TLS

No subjects in Safety Pool 01 R/R FL and Safety Pool 01+04 R/R FL had an AESI of CTLS. There were 7 subjects in Safety Pool 01+04 All B-NHL who reported CTLS, including 3 subjects with MCL, 2 subjects with DLBCL, and 2 subjects with other subtype of large B-cell lymphoma (LBCL). There were 4 (0.9%) subjects with Grade 3 TLS. The median time from diagnosis was 14 days and the median time to resolution was 4.0 days.

Other safety topics of interest

Neurological events

Treatment-emergent neurological events were analyzed using 2 approaches. The first approach used a broad definition that included all TEAEs coded to the MedDRA SOC of nervous system disorders or psychiatric disorders, excluding high-level group terms (HLGTs) of sleep disorders and disturbances and peripheral neuropathies. The second approach summarized neurological events using the definition provided in Topp 2015.

In Safety Pool 01 R/R FL (N=129), using the broad definition for neurological events, 48.1% of subjects had neurological events, and 20.9% of subjects experienced drug-related neurological events. The majority of the neurological events were Grade 1 (27.9%) or Grade 2 (17.8%). Three (2.3%)

subjects experienced Grade 3 neurological events, including Bell's palsy, dizziness, and syncope (1 subject each). Most of the neurological events using the broad definition occurred during the initial 2 cycles of treatment (Week ≤ 8), with a median time to onset of 23.5 days. The majority (59.7%) of subjects experienced only 1 neurological event. Of the 62 subjects who reported neurological events based on the broad definition, 26 (41.9%) subjects required treatment, and 39 (62.9%) subjects had neurological events that resolved, with a median time to resolution of 15.0 days.

Table 36: Summary of Treatment-Emergent Neurological Events Using the Broad Definition Reported for ≥ 1% of Subjects in Any Group by SOC and PT

	GCT3013-01 ESC+EXP	GCT3013-01 ESC+EXP and GCT3013-04 ESC+EXP	
System Organ Class Preferred Term	**R/R FL (N=129)**	**R/R FL (N=151)**	**All B-NHL (N=449)**
Subjects with at least one neurological event (broad definition)	62 (48.1%)	69 (45.7%)	184 (41.0%)
Nervous system disorders	57 (44.2%)	62 (41.1%)	162 (36.1%)
Headache	25 (19.4%)	26 (17.2%)	58 (12.9%)
Dizziness	15 (11.6%)	16 (10.6%)	34 (7.6%)
Immune effector cell-associated neurotoxicity syndrome	8 (6.2%)	8 (5.3%)	28 (6.2%)
Paraesthesia	6 (4.7%)	6 (4.0%)	17 (3.8%)
Balance disorder	3 (2.3%)	3 (2.0%)	3 (0.7%)
Lethargy	3 (2.3%)	3 (2.0%)	6 (1.3%)
Tremor	3 (2.3%)	3 (2.0%)	10 (2.2%)
Neuralgia	2 (1.6%)	2 (1.3%)	4 (0.9%)
Hypoaesthesia	1 (0.8%)	2 (1.3%)	7 (1.6%)
Post herpetic neuralgia	1 (0.8%)	3 (2.0%)	6 (1.3%)
Sciatica	1 (0.8%)	1 (0.7%)	5 (1.1%)
Syncope	1 (0.8%)	2 (1.3%)	4 (0.9%)
Dysgeusia	0	0	6 (1.3%)
Psychiatric disorders	16 (12.4%)	18 (11.9%)	46 (10.2%)
Anxiety	6 (4.7%)	6 (4.0%)	12 (2.7%)
Depression	4 (3.1%)	4 (2.6%)	8 (1.8%)
Agitation	2 (1.6%)	3 (2.0%)	7 (1.6%)
Irritability	2 (1.6%)	2 (1.3%)	2 (0.4%)
Confusional state	1 (0.8%)	1 (0.7%)	8 (1.8%)
Hallucination	1 (0.8%)	2 (1.3%)	4 (0.9%)

B-NHL = B-cell non-Hodgkin lymphoma; ESC = Escalation; EXP = Expansion; FL = follicular lymphoma; ISS = Integrated Summary of Safety; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; R/R = relapsed or refractory; SOC = System Organ Class; TEAE = treatment-emergent adverse event; v = version
Note: Percentages calculated based on N.
Adverse events are classified using MedDRA v26.0 and are counted only once per system organ class and only once per preferred term.
Refer to ISS Table 3.0 for list of search criteria used for neurologic events (broad definition).
Source: ISS Table 5.15

Using the Topp definition, 31.8% of subjects experienced at least 1 neurological event, and 14.0% of subjects experienced drug-related events. All subjects with neurological events per Topp definition experienced Grade 1 or 2 events, except for the 3 (2.3%) subjects who experienced Grade 3 events discussed above. Of the 41 subjects who reported neurological events based on the Topp definition, the majority (75.6%) of subjects experienced 1 neurological event. Most of the neurological events using the Topp definition occurred during the initial 2 cycles of treatment (Week ≤ 8), with a median time to onset of 29.0 days. Overall, 9 (22.0%) subjects required treatment, and 26 (63.4%) subjects had neurological events that resolved, with a median time to resolution of 4.5 days.

Table 37: Summary of Treatment-Emergent Neurological Events Using the Topp Definition Reported for ≥ 1% of Subjects in Any Group by SOC and PT

	GCT3013-01 ESC+EXP	GCT3013-01 ESC+EXP and GCT3013-04 ESC+EXP	
System Organ Class Preferred Term	**R/R FL (N=129)**	**R/R FL (N=151)**	**All B-NHL (N=449)**
Subjects with at least one neurological event (Topp definition)	41 (31.8%)	47 (31.1%)	134 (29.8%)
Nervous system disorders	40 (31.0%)	45 (29.8%)	123 (27.4%)
Dizziness	15 (11.6%)	16 (10.6%)	34 (7.6%)
Immune effector cell-associated neurotoxicity syndrome	8 (6.2%)	8 (5.3%)	28 (6.2%)
Paraesthesia	6 (4.7%)	6 (4.0%)	17 (3.8%)
Balance disorder	3 (2.3%)	3 (2.0%)	3 (0.7%)
Lethargy	3 (2.3%)	3 (2.0%)	6 (1.3%)
Tremor	3 (2.3%)	3 (2.0%)	10 (2.2%)
Neuralgia	2 (1.6%)	2 (1.3%)	4 (0.9%)
Hypoaesthesia	1 (0.8%)	2 (1.3%)	7 (1.6%)
Post herpetic neuralgia	1 (0.8%)	3 (2.0%)	6 (1.3%)
Syncope	1 (0.8%)	2 (1.3%)	4 (0.9%)
Dysgeusia	0	0	6 (1.3%)
Psychiatric disorders	3 (2.3%)	4 (2.6%)	20 (4.5%)
Confusional state	1 (0.8%)	1 (0.7%)	8 (1.8%)
Hallucination	1 (0.8%)	2 (1.3%)	4 (0.9%)

B-NHL = B-cell non-Hodgkin lymphoma; ESC = Escalation; EXP = Expansion; FL = follicular lymphoma; ISS = Integrated Summary of Safety; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; R/R = relapsed or refractory; SOC = System Organ Class; TEAE = treatment-emergent adverse event; v = version
Note: Percentages calculated based on N.
Adverse events are classified using MedDRA v26.0 and are counted only once per system organ class and only once per preferred term.
Refer to ISS Table 3.0 for list of search criteria used for neurologic events (Topp definition).
Source: ISS Table 5.18

In Safety Pool 01+04 R/R All B-NHL (N=449), using the broad definition, 41.0% of subjects experienced at least 1 neurological event. One (0.2%) subject with MCL experienced Grade 4 and 2 (0.4%) subjects (1 with DLBCL and 1 with MCL) reported Grade 5 neurological events (all ICANS) (compared with 0 subjects with Grade 4 or 5 events in Safety Pool 01 R/R FL). Three (0.7%) subjects reported neurological events per broad definition that led to treatment discontinuation (compared with 0 subjects in Safety Pool 01 R/R FL). Using the Topp definition,30.6% of subjects required treatment (compared with 22.0% in Safety Pool 01 R/R FL). The median time to resolution was 9.0 days (compared with 4.5 days in Safety Pool 01 R/R FL). Two (0.4%) subjects experienced neurological events per Topp definition that led to treatment discontinuation (compared with 0 subjects in Safety Pool 01 R/R FL).

Cytopenia events

The description below focuses on the following terms: cytopenia (broad), neutropenia (grouped), febrile neutropenia, thrombocytopenia (broad), anemia (broad), and lymphopenia (grouped). In the case of recurring Grade ≥3 neutropenia, use of growth factors was mandated (Table 38).

Table 38: Subject-Level Summary of Treatment-Emergent Cytopenias

	GCT3013-01 ESC+EXP	GCT3013-01 ESC+EXP and GCT3013-04 ESC+EXP	
	R/R FL (N=129)	R/R FL (N=151)	All B-NHL (N=449)
Cytopenia (broad)			
Subjects with at least one event	60 (46.5%)	70 (46.4%)	235 (52.3%)
Grade 1	5 (3.9%)	5 (3.3%)	14 (3.1%)
Grade 2	7 (5.4%)	9 (6.0%)	27 (6.0%)
Grade 3	21 (16.3%)	23 (15.2%)	79 (17.6%)
Grade 4	26 (20.2%)	32 (21.2%)	114 (25.4%)
Grade 5	1 (0.8%)[b]	1 (0.7%)[b]	1 (0.2%)[b]
Number of episodes per subject[a]			
1 event	26 (43.3%)	31 (44.3%)	83 (35.3%)
2 events	13 (21.7%)	14 (20.0%)	51 (21.7%)
3 events	8 (13.3%)	10 (14.3%)	35 (14.9%)
≥ 4 events	13 (21.7%)	15 (21.4%)	66 (28.1%)
Neutropenia (grouped)			
Subjects with at least one event	36 (27.9%)	44 (29.1%)	145 (32.3%)
Grade 1	0	0	5 (1.1%)
Grade 2	4 (3.1%)	6 (4.0%)	16 (3.6%)
Grade 3	16 (12.4%)	18 (11.9%)	58 (12.9%)
Grade 4	16 (12.4%)	20 (13.2%)	66 (14.7%)
Number of episodes per subject[a]			
1 event	22 (61.1%)	27 (61.4%)	82 (56.6%)
2 events	5 (13.9%)	6 (13.6%)	21 (14.5%)
3 events	5 (13.9%)	5 (11.4%)	15 (10.3%)
≥ 4 events	4 (11.1%)	6 (13.6%)	27 (18.6%)
Subjects with G-CSF treatment required[a]	23 (63.9%)	28 (63.6%)	95 (65.5%)
Febrile neutropenia			
Subjects with at least one event	4 (3.1%)	5 (3.3%)	12 (2.7%)
Grade 2	0	0	1 (0.2%)
Grade 3	4 (3.1%)	5 (3.3%)	11 (2.4%)
Number of episodes per subject[a]			
1 event	3 (75.0%)	4 (80.0%)	11 (91.7%)
2 events	1 (25.0%)	1 (20.0%)	1 (8.3%)
Subjects with G-CSF treatment required[a]	3 (75.0%)	3 (60.0%)	10 (83.3%)
Thrombocytopenia (broad)			
Subjects with at least one event	16 (12.4%)	16 (10.6%)	78 (17.4%)
Grade 1	5 (3.9%)	5 (3.3%)	22 (4.9%)
Grade 2	4 (3.1%)	4 (2.6%)	9 (2.0%)
Grade 3	2 (1.6%)	2 (1.3%)	24 (5.3%)
Grade 4	5 (3.9%)	5 (3.3%)	23 (5.1%)
Number of episodes per subject[a]			
1 event	11 (68.8%)	11 (68.8%)	60 (76.9%)
2 events	4 (25.0%)	4 (25.0%)	13 (16.7%)
3 events	1 (6.3%)	1 (6.3%)	3 (3.8%)
≥ 4 events	0	0	2 (2.6%)
Subjects with treatment required[a]	2 (12.5%)	2 (12.5%)	23 (29.5%)
Anemia (broad)			
Subjects with at least one event	19 (14.7%)	19 (12.6%)	80 (17.8%)
Grade 1	4 (3.1%)	4 (2.6%)	15 (3.3%)
Grade 2	7 (5.4%)	7 (4.6%)	20 (4.5%)
Grade 3	8 (6.2%)	8 (5.3%)	45 (10.0%)
Number of episodes per subject[a]			
1 event	15 (78.9%)	15 (78.9%)	63 (78.8%)
2 events	3 (15.8%)	3 (15.8%)	14 (17.5%)

	GCT3013-01 ESC+EXP	GCT3013-01 ESC+EXP and GCT3013-04 ESC+EXP	
	R/R FL (N=129)	R/R FL (N=151)	All B-NHL (N=449)
≥ 4 events	1 (5.3%)	1 (5.3%)	3 (3.8%)
Subjects with treatment required[a]	6 (31.6%)	6 (31.6%)	40 (50.0%)
Lymphopenia (grouped)			
Subjects with at least one event	16 (12.4%)	19 (12.6%)	54 (12.0%)
Grade 1	1 (0.8%)	1 (0.7%)	1 (0.2%)
Grade 2	1 (0.8%)	1 (0.7%)	4 (0.9%)
Grade 3	5 (3.9%)	6 (4.0%)	13 (2.9%)
Grade 4	9 (7.0%)	11 (7.3%)	36 (8.0%)
Number of episodes per subject[a]			
1 event	13 (81.3%)	15 (78.9%)	34 (63.0%)
2 events	3 (18.8%)	4 (21.1%)	12 (22.2%)
3 events	0	0	5 (9.3%)
≥ 4 events	0	0	3 (5.6%)
Subjects with treatment required[a]	0	0	0

B-NHL = B-cell non-Hodgkin lymphoma; ESC = Escalation; EXP = Expansion; FL = follicular lymphoma; G-CSF = granulocyte colony-stimulating factor; ISS = Integrated Summary of Safety; R/R = relapsed or refractory
a. Percentage calculated based on subjects with at least 1 event.
b. Grade 5 cytopenia was reported in 1 subject in Study GCT3013-01 Expansion Part iNHL cohort with pre-existing MDS confirmed after enrollment who discontinued shortly after enrollment due to worsening of MDS and later died due to progression of MDS (Study GCT3013-01-EXP-iNHL CSR Appendix 16.2.7.3).
Note: The toxicity grade refers to the worst toxicity grade per subject.
Refer to ISS Table 3.0 for list of search criteria used for cytopenias.
Source: ISS Table 5.27

For neutropenia, the median time from first dose to first onset was 63.5 days (range: 7, 450), and the median time to resolution was 27.5 days (range: 3, 415). A total of 23 (63.9%) subjects required granulocyte colony-stimulating factor (G-CSF) treatment. For febrile neutropenia the median time to onset was 122.0 days (range: 71, 346), and the median time to resolution was 6.5 days (range: 3, 17). Three (75.0%) subjects required G-CSF treatment. For thrombocytopenia the median time to onset was 21.0 days (range: 2, 367), and the median time to resolution was 15.0 days (range: 7, 140). A total of 12.5% of subjects required treatment. For anemia the median time from to onset was 43.0 days (range: 2, 243), and the median time to resolution was 11.0 days (range: 1, 167). A total of 31.6% of subjects required treatment. For lymphopenia the median time to onset was 15.5 days (range, 7, 245) and the median time to resolution was 15.0 days (range: 7, 100). No subjects required treatment.

Cytopenia overall (as well as thrombocytopenia [broad], and anemia [broad], and lymphopenia [grouped]) were reported at higher incidences during the first 8 weeks of treatment compared with the other analysis periods, whereas the incidences of neutropenia (grouped) and febrile neutropenia were more evenly distributed throughout the various analysis periods.

Serious infections

In Safety Pool 01 R/R FL (N=129), 52 (40.3%) subjects experienced at least 1 serious infection, with the most frequently reported PTs (in ≥ 5% of subjects) being COVID-19 (11.6%), COVID 19 pneumonia (7.8%), and pneumonia (5.4%). Serious events in the SOC of Infections and Infestations were considered related to epcoritamab by the investigator in 12 (9.3%) subjects. Fatal events were reported in 8 (6.2%) subjects; none of the fatal serious infections were considered related to epcoritamab by the investigator. Serious infections leading to treatment discontinuation were reported in 14 (10.9%) subjects and events leading to dose delay were reported in 32 (24.8%) subjects. The median time from first dose to first onset was 101.5 days. The majority of serious infections were reported after Week 36 (Cycle 10+), primarily driven by COVID-19 events. Almost all subjects with serious infections required treatment and 71.2% of subjects had serious infections that resolved with a median time to resolution of 20.0 day.

In Safety Pool 01+04 All B-NHL (N=449), 34.7% of subjects experienced at least 1 serious infection. Six subjects experienced Grade 4 serious infections (compared with 0 subjects in Safety Pool 01 R/R FL). Of the 30 subjects with Grade 5 serious infections, 2 subjects had events that were considered related to study drug, including COVID-19 pneumonia and pneumonia bacterial (1 subject each) (compared with no drug-related serious infections in Safety Pool 01 R/R FL). The median time to first onset was longer compared with that in Safety Pool 01 R/R FL (120 days vs 101.5 days).

Table 39: Subject-Level Summary of Treatment-Emergent Serious Infections

	GCT3013-01 ESC+EXP	**GCT3013-01 ESC+EXP and GCT3013-04 ESC+EXP**	
	R/R FL (N=129)	**R/R FL (N=151)**	**All B-NHL (N=449)**
Subjects with at least one event	52 (40.3%)	60 (39.7%)	156 (34.7%)
Grade 1	0	0	1 (0.2%)
Grade 2	5 (3.9%)	7 (4.6%)	11 (2.4%)
Grade 3	39 (30.2%)	45 (29.8%)	108 (24.1%)
Grade 4	0	0	6 (1.3%)
Grade 5	8 (6.2%)	8 (5.3%)	30 (6.7%)
Number of episodes per subject[a]			
1 event	37 (71.2%)	42 (70.0%)	109 (69.9%)
2 events	10 (19.2%)	12 (20.0%)	34 (21.8%)
3 events	4 (7.7%)	5 (8.3%)	9 (5.8%)
≥ 4 events	1 (1.9%)	1 (1.7%)	4 (2.6%)
Subjects with treatment required[a]	50 (96.2%)	57 (95.0%)	148 (94.9%)
Time from first dose to first onset (days)			
n	52	60	156
Median	101.5	133.0	120.0
Min, max	1, 636	1, 636	1, 787
Time to resolution (days)[b,c]			
Subjects with resolved events[a]	37 (71.2%)	42 (70.0%)	101 (64.7%)
Median	20.0	21.5	20.0
Min, max	5, 249	5, 249	4, 413

B-NHL = B-cell non-Hodgkin lymphoma; ESC = Escalation; EXP = Expansion; FL = follicular lymphoma; ISS = Integrated Summary of Safety; max = maximum; min = minimum; R/R = relapsed or refractory
a. Percentage calculated based on subjects with at least 1 event.
b. Based on longest duration recorded in subjects with multiple events.
c. For subjects with multiple events, all events must be resolved.
Note: The toxicity grade refers to the worst toxicity grade per subject.
Refer to ISS Table 3.0 for list of search criteria used for serious infections.
Source: ISS Table 5.25

With the response to the first LoQ, updated safety data on serious infections has been provided (DCO16Oct2023).

Table 40: Treatment-emergent Serious Infections Reported in ≥ 2% of Subjects in Any Safety Pool by PT (Initial vs. Update - 48mg Dose - Studies GCT3013-01 and GCT3013-04 - Safety Analysis Set)

System Organ Class Preferred Term	GCT3013-01 ESC+EXP R/R FL		GCT3013-01 and GCT3013-04 ESC+EXP R/R FL		GCT3013-01 and GCT3013-04 ESC+EXP All B-NHL	
	Initial (N=129) n (%)	Update (N=129) n (%)	Initial (N=151) n (%)	Update (N=151) n (%)	Initial (N=449) n (%)	Update (N=449) n (%)
Subjects with at least one serious infection	**52 (40.3%)**	**55 (42.6%)**	**60 (39.7%)**	**65 (43.0%)**	**156 (34.7%)**	**165 (36.7%)**
Infections and infestations	**52 (40.3%)**	**55 (42.6%)**	**60 (39.7%)**	**65 (43.0%)**	**156 (34.7%)**	**165 (36.7%)**
COVID-19	15 (11.6%)	18 (14.0%)	16 (10.6%)	20 (13.2%)	40 (8.9%)	44 (9.8%)
COVID-19 pneumonia	10 (7.8%)	12 (9.3%)	11 (7.3%)	15 (9.9%)	33 (7.3%)	38 (8.5%)
Pneumonia	7 (5.4%)	8 (6.2%)	8 (5.3%)	9 (6.0%)	21 (4.7%)	24 (5.3%)
Pneumocystis jirovecii pneumonia	3 (2.3%)	3 (2.3%)	3 (2.0%)	3 (2.0%)	4 (0.9%)	4 (0.9%)
Herpes zoster	1 (0.8%)	1 (0.8%)	3 (2.0%)	3 (2.0%)	6 (1.3%)	6 (1.3%)

Source tables: Data Update Table 5.2, Table 5.2su, FL ISS Table 5.2.

Table 41: Treatment-emergent Fatal Infections in Any Safety Pool by PT (Initial vs. Update - 48mg Dose Studies GCT3013-01 and GCT3013-04 - Safety Analysis Set)

System Organ Class Preferred Term	GCT3013-01 ESC+EXP R/R FL		GCT3013-01 and GCT3013-04 ESC+EXP R/R FL		GCT3013-01 and GCT3013-04 ESC+EXP All B-NHL	
	Initial (N=129) n (%)	Update (N=129) n (%)	Initial (N=151) n (%)	Update (N=151) n (%)	Initial l (N=449) n (%)	Update (N=449) n (%)
Subjects with at least one fatal infection	**8 (6.2%)**	**9 (7.0%)**	**8 (5.3%)**	**9 (6.0%)**	**31 (6.9%)**	**32 (7.1%)**
Infections and infestations	**8 (6.2%)**	**9 (7.0%)**	**8 (5.3%)**	**9 (6.0%)**	**31 (6.9%)**	**32 (7.1%)**
COVID-19 pneumonia	5 (3.9%)	5 (3.9%)	5 (3.3%)	5 (3.3%)	17 (3.8%)	17 (3.8%)
Pseudomonal sepsis	1 (0.8%)	2 (1.6%)	1 (0.7%)	2 (1.3%)	1 (0.2%)	2 (0.4%)
COVID-19	1 (0.8%)	1 (0.8%)	1 (0.7%)	1 (0.7%)	6 (1.3%)	6 (1.3%)
Pneumonia	1 (0.8%)	1 (0.8%)	1 (0.7%)	1 (0.7%)	2 (0.4%)	2 (0.4%)
Necrotising fasciitis	0	0	0	0	1 (0.2%)	1 (0.2%)
Pneumonia bacterial	0	0	0	0	1 (0.2%)	1 (0.2%)
Progressive multifocal leukoencephalopathy	0	0	0	0	1 (0.2%)	1 (0.2%)
Septic shock	0	0	0	0	2 (0.4%)	2 (0.4%)

Source tables: Data Update Table 3.25, Table 3.25su, FL ISS Table 3.25.

Table 42: Subject-Level Summary of Treatment-Emergent Serious Infections in All Safety Pools

	GCT3013-01 ESC+EXP		GCT3013-01 ESC+EXP and GCT3013-04 ESC+EXP			
	R/R FL (N=129)		R/R FL (N=151)		All B-NHL (N=449)	
	Initial	Update	Initial	Update	Initial	Update
Subjects with at least one TEAE	52 (40.3%)	55 (42.6%)	60 (39.7%)	65 (43.0%)	156 (34.7%)	165 (36.7%)
Drug-related TEAE	12 (9.3%)	13 (10.1%)	17 (11.3%)	19 (12.6%)	36 (8.0%)	43 (9.6%)
Grade 3 and higher TEAE	47 (36.4%)	51 (39.5%)	53 (35.1%)	58 (38.4%)	144 (32.1%)	154 (34.3%)
Grade 3 and higher drug related TEAE	10 (7.8%)	11 (8.5%)	13 (8.6%)	14 (9.3%)	32 (7.1%)	38 (8.5%)
Grade 3 or 4 TEAE	41 (31.8%)	45 (34.9%)	47 (31.1%)	52 (34.4%)	123 (27.4%)	132 (29.4%)
Grade 3 or 4 drug-related TEAE	10 (7.8%)	11 (8.5%)	13 (8.6%)	14 (9.3%)	30 (6.7%)	36 (8.0%)

Injection site reactions

In Safety Pool 01 R/R FL (N=129), 56.6% of subjects experienced at least 1 TEAE of injection site reaction, all of which were drug-related (Table 43). The most frequently reported (≥ 5% of subjects) events included injection site reaction (36.4%), injection site erythema (17.8%), and injection site rash (7.8%). Three (2.3%) subjects experienced injection site reactions leading to dose delay. No subject experienced injection site reactions leading to treatment discontinuation. Of the 73 subjects

who experienced injection site reactions in Safety Pool 01 R/R FL, 33 (45.2%) subjects used at least 1 concomitant medication for treating injection site reactions. The most commonly used (in ≥ 5% of subjects) concomitant medications for treating injection site reactions included hydrocortisone (topical) and cetirizine (6.8% each) and loratadine (5.5%). In the other safety pools also cetirizine and clobetasol propionate were used to treat injection site reactions.

Table 43: Subject-Level Summary of Treatment-Emergent Injection Site Reactions

	GCT3013-01 ESC+EXP	GCT3013-01 ESC+EXP and GCT3013-04 ESC+EXP	
	R/R FL (N=129)	R/R FL (N=151)	All B-NHL (N=449)
Subjects with at least one event	73 (56.6%)	89 (58.9%)	203 (45.2%)
Grade 1	53 (41.1%)	69 (45.7%)	165 (36.7%)
Grade 2	20 (15.5%)	20 (13.2%)	38 (8.5%)
Number of episodes per subject[a]			
1 event	27 (37.0%)	33 (37.1%)	77 (37.9%)
2 events	16 (21.9%)	19 (21.3%)	35 (17.2%)
3 events	5 (6.8%)	6 (6.7%)	14 (6.9%)
≥ 4 events	25 (34.2%)	31 (34.8%)	77 (37.9%)
Subjects with treatment required[a]	36 (49.3%)	44 (49.4%)	75 (36.9%)
Time from first dose to first onset (days)			
n	73	89	203
Median	29.0	24.0	18.0
Min, max	1, 213	1, 213	1, 610
Time to resolution (days)[b,c]			
Subjects with resolved events[a]	67 (91.8%)	81 (91.0%)	186 (91.6%)
Median	14.0	14.0	14.5
Min, max	1, 485	1, 507	1, 507

B-NHL = B-cell non-Hodgkin lymphoma; ESC = Escalation; EXP = Expansion; FL = follicular lymphoma; ISS = Integrated Summary of Safety; max = maximum; min = minimum; R/R = relapsed or refractory
Note: The toxicity grade refers to the worst toxicity grade per subject.
Refer to ISS Table 3.0 for list of search criteria used for injection site reactions.
a. Percentage calculated based on number of subjects with at least 1 event.
b. Based on longest duration recorded in subjects with multiple events.
c. For subjects with multiple events, all events must be resolved.
Source: ISS Table 5.32

Other events

In Safety Pool 01 R/R FL (N=129), 32 (24.8%) subjects experienced at least one event of pyrexia, of which 16 (12.4%) subjects experienced drug-related events. Grade 3 events were reported in 3 (2.3%) subjects. Eighteen (56.3%) subjects required treatment. The median time from first dose to first onset was 22.0 days (range: 1, 307) and median time to resolution was 2.5 days (range: 1, 147). The majority (27 subjects, 20.9%) of pyrexia events were reported in the first 8-week analysis period.

In Safety Pool 01 R/R FL (N=129) and Safety Pool 01+04 R/R FL (N =151), no subject experienced treatment-emergent tumour flare. In Safety Pool 01+04 All B-NHL, 7 (1.6%) subjects experienced tumour flare, including 6 (1.3%) subjects who experienced drug-related events. All 7 subjects experienced Grade 2 events. Four (57.1%) subjects required treatment and 6 (85.7%) subjects had resolved events. The median time from first dose to first onset was 16.0 days (range: 5, 34) with median time to resolution of 22.5 days (range: 1, 54) (ISS Table 5.36). One subject had tumour flare leading to dose delay.

No subject experienced treatment-emergent hemophagocytic lymphohistiocytosis events in any safety pool.

AEs leading to dose delay

In Safety Pool 01 R/R FL (N=129), 59.7% of subjects experienced at least 1 TEAE leading to dose delay; in 34.9% of subjects, events were considered drug-related. The most frequently reported (in ≥ 5% of subjects) TEAEs leading to dose delay included COVID-19 (21.7%, 4.7% assessed as drug-related) and CRS (11.6%, all drug-related). Other frequently reported TEAEs were pneumonia (4.7%), upper respiratory tract infection (4.7%) and neutropenia (4.7%). In Safety Pool 01+04 All B-NHL (N=449), TEAEs leading to dose delay were reported for 52.6% of subjects. The frequency of TEAEs and drug-related TEAEs leading to dose delay were similar to those reported for Safety Pool 01 R/R FL. In addition to COVID-19 and CRS, neutropenia (5.1%) was also a frequently reported TEAE that led to dose delay.

Overdose

As of the 21 April 2023 data cutoff date, 1 medication error has been reported in FL subjects receiving epcoritamab monotherapy across the Primary Safety Analysis Set of Safety Pool 01 R/R FL and the Supportive Safety Analysis Set of Safety Pool 01+04 R/R FL. This medication error was an overdose (> 10% protocol-prescribed dose) in the priming dose during the Escalation Part of Study GCT3013-01; the intended epcoritamab dose was 0.08 mg, but the subject was administered a dose of 0.96 mg. There were no adverse events reported due to this overdose. In Dose Escalation, 3 subjects received a full planned dose of 60 mg with no unexpected adverse effects.

In the event of overdose, subjects should be monitored for any signs or symptoms of adverse reactions and managed appropriately with supportive treatment.

COVID-19

Studies GCT3013-01 and GCT3013-04 were conducted at the peak of the COVID 19 pandemic and at a time when the highly infectious Omicron variants were prevalent globally. Subjects were at higher risk of COVID-19 infection and severe outcomes than the general population due to their underlying R/R lymphoma, advanced age, as well as prior and ongoing cancer treatment. Additional exploratory analyses were conducted to examine the impact of COVID-19 on the safety results from subjects with FL in the iNHL Expansion Part of Study GCT3013 01.

The safety results from subjects with FL in the iNHL Expansion Part of Study GCT3013 01 (Study GCT3013-01-EXP-iNHL) are reported here. Of the 39 (25.2%) subjects in the iNHL expansion cohort who died during the study (including during the survival follow-up period), nearly half (17/39) of subjects had a death associated with COVID-19, including 14 (10.9%) subjects with FL and 3 (11.1%) subjects with other iNHL subtypes. All but 2 of these 17 fatal cases in the iNHL expansion cohort, including 13 of 14 fatal cases in subjects with FL, occurred in subjects ≥ 65 years of age. The median age of the 14 subjects with FL who died was 73.0 years, with 4 (28.6%) subjects ≥75 years of age. In contrast, the median age of 74 subjects with FL who did not experience COVID-19 was 63.5 years, with 12 (16.2%) subjects ≥75 years of age. These results are consistent with findings that age is a strong risk factor for severe COVID-19 outcomes.

Laboratory findings

Shifts from baseline CTCAE grade to worst on-treatment CTCAE grade for hematology and coagulation parameters are provided in Table 44.

Table 44: Worsened from Baseline to On-Treatment CTCAE Grade

	GCT3013-01 ESC+EXP	GCT3013-01 ESC+EXP and GCT3013-04 ESC+EXP	
CTCAE Grade	**R/R FL (N=129)**	**R/R FL (N=151)**	**All B-NHL (N=449)**
Hemoglobin (Hypo)			
n	129	151	447
Grade 1	37 (28.7%)	49 (32.5%)	98 (21.9%)
Grade 2	26 (20.2%)	28 (18.5%)	118 (26.4%)
Grade 3	13 (10.1%)	13 (8.6%)	67 (15.0%)
All Grades	76 (58.9%)	90 (59.6%)	283 (63.3%)
Absolute Neutrophils Count (Hypo)			
n	127	149	439
Grade 1	9 (7.1%)	11 (7.4%)	28 (6.4%)
Grade 2	22 (17.3%)	28 (18.8%)	62 (14.1%)
Grade 3	17 (13.4%)	22 (14.8%)	76 (17.3%)
Grade 4	21 (16.5%)	26 (17.4%)	80 (18.2%)
Grade 3/4	38 (29.9%)	48 (32.2%)	156 (35.5%)
All Grades	69 (54.3%)	87 (58.4%)	246 (56.0%)
Absolute Lymphocytes Count (Hyper)			
n	125	147	426
Grade 2	8 (6.4%)	9 (6.1%)	32 (7.5%)
Grade 3	0	0	5 (1.2%)
All Grades	8 (6.4%)	9 (6.1%)	37 (8.7%)
Absolute Lymphocytes Count (Hypo)			
n	125	147	426
Grade 1	5 (4.0%)	5 (3.4%)	8 (1.9%)
Grade 2	9 (7.2%)	10 (6.8%)	26 (6.1%)
Grade 3	37 (29.6%)	45 (30.6%)	123 (28.9%)
Grade 4	65 (52.0%)	76 (51.7%)	224 (52.6%)
Grade 3/4	102 (81.6%)	121 (82.3%)	347 (81.5%)
All Grades	116 (92.8%)	136 (92.5%)	381 (89.4%)
White Blood Cell Count (Hypo)			
n	129	151	447
Grade 1	17 (13.2%)	19 (12.6%)	60 (13.4%)
Grade 2	32 (24.8%)	43 (28.5%)	98 (21.9%)
Grade 3	19 (14.7%)	24 (15.9%)	83 (18.6%)
Grade 4	5 (3.9%)	5 (3.3%)	26 (5.8%)
Grade 3/4	24 (18.6%)	29 (19.2%)	109 (24.4%)
All Grades	73 (56.6%)	91 (60.3%)	267 (59.7%)
Platelets (Hypo)			
n	129	151	447
Grade 1	36 (27.9%)	44 (29.1%)	128 (28.6%)
Grade 2	16 (12.4%)	16 (10.6%)	45 (10.1%)
Grade 3	5 (3.9%)	5 (3.3%)	42 (9.4%)
Grade 4	5 (3.9%)	5 (3.3%)	27 (6.0%)
Grade 3/4	10 (7.8%)	10 (6.6%)	69 (15.4%)
All Grades	62 (48.1%)	70 (46.4%)	242 (54.1%)
International Normalized Ratio (elevated)			
n	128	150	436
Grade 1	15 (11.7%)	15 (10.0%)	66 (15.1%)
Grade 2	8 (6.3%)	8 (5.3%)	22 (5.0%)
Grade 3	2 (1.6%)	2 (1.3%)	6 (1.4%)
All Grades	25 (19.5%)	25 (16.7%)	94 (21.6%)

CTCAE Grade	GCT3013-01 ESC+EXP R/R FL (N=129)	GCT3013-01 ESC+EXP and GCT3013-04 ESC+EXP R/R FL (N=151)	GCT3013-01 ESC+EXP and GCT3013-04 ESC+EXP All B-NHL (N=449)
Activated Partial Thromboplastin Time (elevated)			
n	101	123	370
Grade 1	18 (17.8%)	19 (15.4%)	83 (22.4%)
Grade 2	2 (2.0%)	2 (1.6%)	7 (1.9%)
Grade 3	5 (5.0%)	5 (4.1%)	9 (2.4%)
All Grades	25 (24.8%)	26 (21.1%)	99 (26.8%)

B-NHL = B-cell non-Hodgkin lymphoma; ESC = Escalation; EXP = Expansion; FL = follicular lymphoma; ISS = Integrated Summary of Safety; R/R = relapsed or refractory
CTCAE: Common Terminology Criteria for Adverse Events 5.0.
Note: Percentages calculated based on n (number of subjects with baseline and at least one on-treatment lab value).
Source: ISS Table 6.1

Worsening biochemistry parameters in CTCAE grades to Grade 3 or 4 is reflected below (Table 45).

Table 45: Summary of Biochemistry Laboratory Results – Worsened from Baseline to On-Treatment CTCAE Grade

CTCAE Grade	GCT3013-01 ESC+EXP R/R FL (N=129)	GCT3013-01 ESC+EXP and GCT3013-04 ESC+EXP R/R FL (N=151)	GCT3013-01 ESC+EXP and GCT3013-04 ESC+EXP All B-NHL (N=449)
Albumin (Hypo)			
n	129	151	445
Grade 3	4 (3.1%)	4 (2.6%)	13 (2.9%)
All Grades	78 (60.5%)	97 (64.2%)	303 (68.1%)
Alanine Aminotransferase (Hyper)			
n	129	151	446
Grade 3	9 (7.0%)	12 (7.9%)	25 (5.6%)
Grade 4	1 (0.8%)	2 (1.3%)	2 (0.4%)
Grade 3/4	10 (7.8%)	14 (9.3%)	27 (6.1%)
All Grades	60 (46.5%)	77 (51.0%)	216 (48.4%)
Aspartate Transaminase (Hyper)			
n	129	151	444
Grade 3	5 (3.9%)	6 (4.0%)	15 (3.4%)
Grade 4	2 (1.6%)	2 (1.3%)	3 (0.7%)
Grade 3/4	7 (5.4%)	8 (5.3%)	18 (4.1%)
All Grades	57 (44.2%)	70 (46.4%)	214 (48.2%)
Alkaline Phosphatase (Hyper)			
n	129	151	446
Grade 3	0	0	3 (0.7%)
Grade 4	0	0	0
Grade 3/4	0	0	3 (0.7%)
All Grades	38 (29.5%)	46 (30.5%)	153 (34.3%)
Magnesium (Hyper)			
n	129	151	441
Grade 3	1 (0.8%)	1 (0.7%)	6 (1.4%)
Grade 4	0	0	0
Grade 3/4	1 (0.8%)	1 (0.7%)	6 (1.4%)
All Grades	10 (7.8%)	15 (9.9%)	53 (12.0%)
Magnesium (Hypo)			
n	129	151	441
Grade 3	0	0	0
Grade 4	1 (0.8%)	1 (0.7%)	1 (0.2%)
Grade 3/4	1 (0.8%)	1 (0.7%)	1 (0.2%)

	GCT3013-01 ESC+EXP	GCT3013-01 ESC+EXP and GCT3013-04 ESC+EXP	
CTCAE Grade	**R/R FL (N=129)**	**R/R FL (N=151)**	**All B-NHL (N=449)**
All Grades	25 (19.4%)	29 (19.2%)	117 (26.5%)
Sodium (Hypo)			
n	128	150	443
Grade 3	2 (1.6%)	2 (1.3%)	7 (1.6%)
Grade 4	0	0	1 (0.2%)
Grade 3/4	2 (1.6%)	2 (1.3%)	8 (1.8%)
All Grades	65 (50.8%)	78 (52.0%)	258 (58.2%)
Creatinine (Hyper)			
n	129	151	446
Grade 3	0	0	10 (2.2%)
Grade 4	1 (0.8%)	1 (0.7%)	1 (0.2%)
Grade 3/4	1 (0.8%)	1 (0.7%)	11 (2.5%)
All Grades	47 (36.4%)	54 (35.8%)	142 (31.8%)
Total Bilirubin (Hyper)			
n	129	151	446
Grade 3	2 (1.6%)	2 (1.3%)	13 (2.9%)
Grade 4	0	0	1 (0.2%)
Grade 3/4	2 (1.6%)	2 (1.3%)	14 (3.1%)
All Grades	36 (27.9%)	40 (26.5%)	101 (22.6%)
Uric Acid (elevated)			
n	128	150	443
Low/Normal	89 (69.5%)	104 (69.3%)	320 (72.2%)
High	39 (30.5%)	46 (30.7%)	123 (27.8%)
Phosphate (Hyper)			
n	129	151	445
Low/Normal	99 (76.7%)	120 (79.5%)	350 (78.7%)
High	30 (23.3%)	31 (20.5%)	95 (21.3%)
Phosphate (Hypo)			
n	129	151	445
High/Normal	53 (41.1%)	59 (39.1%)	162 (36.4%)
Low	76 (58.9%)	92 (60.9%)	283 (63.6%)
Potassium (Hyper)			
n	129	151	446
Grade 3	1 (0.8%)	2 (1.3%)	9 (2.0%)
Grade 4	1 (0.8%)	1 (0.7%)	3 (0.7%)
Grade 3/4	2 (1.6%)	3 (2.0%)	12 (2.7%)
All Grades	25 (19.4%)	33 (21.9%)	117 (26.2%)
Potassium (Hypo)			
n	129	151	446
Grade 3	3 (2.3%)	4 (2.6%)	20 (4.5%)
Grade 4	1 (0.8%)	1 (0.7%)	2 (0.4%)
Grade 3/4	4 (3.1%)	5 (3.3%)	22 (4.9%)
Calcium (Hypo)			
n	33	44	124
Grade 1	6 (18.2%)	10 (22.7%)	15 (12.1%)
Grade 2	2 (6.1%)	2 (4.5%)	3 (2.4%)
Grade 3	0	0	0
Grade 4	0	0	0
Grade 3/4	0	0	0
All Grades	8 (24.2%)	12 (27.3%)	18 (14.5%)
All Grades	25 (19.4%)	31 (20.5%)	132 (29.6%)
Glucose (Hyper)			
n	128	150	445
Low/Normal	13 (10.2%)	16 (10.7%)	49 (11.0%)
High	114 (89.1%)	133 (88.7%)	394 (88.5%)

	GCT3013-01 ESC+EXP	GCT3013-01 ESC+EXP and GCT3013-04 ESC+EXP	
CTCAE Grade	**R/R FL (N=129)**	**R/R FL (N=151)**	**All B-NHL (N=449)**
Missing	1 (0.8%)	1 (0.7%)	2 (0.4%)
All Grades	18 (14.1%)	22 (14.7%)	68 (15.3%)

B-NHL = B-cell non-Hodgkin lymphoma; ESC = Escalation; EXP = Expansion; FL = follicular lymphoma; ISS = Integrated Summary of Safety; R/R = relapsed or refractory
CTCAE: Common Terminology Criteria for Adverse Events 5.0.
Note: Percentages calculated based on n (number of subjects with baseline and at least one on-treatment lab value).

Source: ISS Table 6.2

Drug-induced liver injury (DILI) (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 alkaline phosphatase 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. All potential events of elevations in ALT, AST, and total bilirubin occurring within a concurrent 30-day period were reviewed and summarized.

In Safety Pool 01 R/R FL (N=129), 3 (2.3%) subjects had AST or ALT > 3 × ULN and total bilirubin > 2 × ULN within 30 days of epcoritamab administration. All these 3 subjects had alternative etiologies for the abnormal hepatic laboratory results, including concurrent CRS (2 subjects) and hepatitis E (1 subject). According to the MAH there was no evidence suggestive of DILI in the 3 cases. Narrative are provided:

- A subjectwith FL and a medical history of hypertension, hypercholesterolemia, and nephrolithiasis had normal LFTs at baseline. On D169 (C7D1), elevated ALT (74 U/L, 1.8×ULN) and AST (52 U/L, 1.3×ULN) were observed, while total bilirubin (8 µmol/L) and ALP (93 U/L) were normal. On D184 (C7D15), the ALT (490 U/L, 11.95×ULN) and AST (338 U/L, 8.45×ULN) levels deteriorated, but the total bilirubin (9 µmol/L) and ALP (102 U/L) remained normal. On D185, the subject was diagnosed with urinary tract infection (Grade 3). On D188, the laboratory data revealed further worsened ALT (573 U/L, 13.98×ULN) and AST (390 U/L, 9.75×ULN), with a normal total bilirubin (18 µmol/L) and ALP (90 U/L). On D198, a diagnosis of hepatitis E (Grade 3) was made with significantly elevated LFTs (ALT 2531 U/L, 50.62×ULN; AST 1768 U/L, 35.36×ULN; total bilirubin 69 µmol/L, 3.29×ULN; and ALP 187 U/L, 1.63×ULN). Due to these findings, the subject was consequently withdrawn from the study.
- A subjectwith FL and relevant medical history of multiple sclerosis had normal AST (19 U/L) and ALT (21 U/L) at baseline (C1D1) but elevated total bilirubin (23 µmol/L, 1.15×ULN). On D16, the subject experienced CRS (Grade 2; requiring IV fluids, piperacillin, and tocilizumab) and lymphopenia (Grade 4), both considered related to epcoritamab by the investigator, and both eventually resolved. On the same day (D16), elevated LFTs were observed with AST (137 U/L, 4.03×ULN), ALT (271 U/L, 4.93×ULN), and total bilirubin (90 µmol/L, 4.5×ULN), with normal ALP (119 U/L). The subject continued treatment with no dose delays. The elevated LFTs of AST and ALT resolved by Day 29 and remained in the normal range, while the total bilirubin generally did not resolve below 2×ULN until D86. ALP remained in the normal range.
- A subjectwith FL and relevant medical history of congestive cardiac failure and ongoing ejection fraction decreased, peripheral edema, and pleural effusion at study entry had normal LFTs at baseline (C1D1) for AST (17 U/L), ALT (12 U/L), and total bilirubin (8.55 µmol/L). On D15, the subject experienced CRS (Grade 2) that resolved on D16 without specific treatment although IV fluids and cefepime were administered for prophylaxis. Elevated LFTs were observed on D15 for AST and ALT (AST 787 U/L, 23.15×ULN; ALT 399 U/L, 8.87×ULN) and total bilirubin (25.65 µmol/L, 1.25×ULN); and with elevations on D16 for AST, ALT, and total bilirubin (AST 296 U/L, 8.71×ULN; ALT 378 U/L, 8.4×ULN; and total bilirubin 58.14 µmol/L,

2.83×ULN). ALP was also elevated >2×ULN on D15 (475 U/L, 3.17×ULN [worst value on D15]) and D16 (401 U/L, 2.67×ULN). The elevated LFTs resolved with the resolution of CRS and remained in the normal range from C2 onward. The subject continued treatment without dose delay and remained ongoing in treatment as of the data cutoff date following administration of the C22D1 dose.

In Safety Pool 01+04 All B-NHL (N=449), 16 (3.6%) subjects had AST/ALT > 3 × ULN and total bilirubin > 2 × ULN within 30 days of epcoritamab administration. In addition to the 3 subjects with FL described in Safety Pool 01 R/R FL, 4 subjects with other iNHL subtypes in Study GCT3013-01 Expansion Part iNHL cohort had abnormal hepatic laboratory tests that met the first 2 laboratory criteria for potential DILI. According to the MAH these 4 subjects had alternative etiologies for the elevated hepatic laboratory results including concurrent CRS events (4 subjects) and underlying prior significant liver diseases or comorbidities (2 subjects). According to the MAH there was no evidence suggestive of DILI in these 4 cases. In Study GCT3013-01 Expansion Part aNHL cohort, 6 (3.6%) subjects with LBCL had AST/ALT > 3 × ULN and total bilirubin > 2 × ULN within 30 days of epcoritamab administration. Out of the 6 subjects, 3 subjects had abnormal hepatic laboratory results in the context of progressive disease, with reported causes of death being either disease progression (n=2) or hepatotoxicity due to disease progression (n=1); 2 subjects experienced abnormal hepatic laboratory results with concurrent Grade 4 pneumonia or neutropenic fever; and 1 subject experienced transient elevated hepatic function tests and resolved along with concurrent TEAEs of CRS.

Three (4.8%) subjects with MCL in Study GCT3013-01 had hepatic laboratory results that met the first 2 laboratory criteria for potential DILI. According to the MAH all these 3 subjects had alternative etiologies for the elevated hepatic laboratory results including CRS (3 subjects), disease progression (1 subject), and significant prior liver disease (1 subject). There was no evidence suggestive of DILI in these 3 cases.

Table 46: Abnormal On-Treatment Hepatic Laboratory Results

	GCT3013-01 ESC+EXP	**GCT3013-01 ESC+EXP and GCT3013-04 ESC+EXP**	
	R/R FL (N=129)	**R/R FL (N=151)**	**All B-NHL (N=449)**
ALT or AST > 3 × ULN	22 (17.1%)	27 (17.9%)	79 (17.6%)
ALT or AST > 5 × ULN	13 (10.1%)	17 (11.3%)	35 (7.8%)
ALT or AST > 10 × ULN	5 (3.9%)	6 (4.0%)	13 (2.9%)
ALT or AST > 20 × ULN	2 (1.6%)	3 (2.0%)	4 (0.9%)
Total Bilirubin > 2 × ULN	5 (3.9%)	6 (4.0%)	28 (6.2%)
Concurrent (1 day) ALT or AST > 3 × ULN and total bilirubin > 2 × ULN	3 (2.3%)	3 (2.0%)	13 (2.9%)
Concurrent (30 days) ALT or AST > 3 × ULN and total bilirubin > 2 × ULN	3 (2.3%)	3 (2.0%)	16 (3.6%)
ALT or AST > 3 × ULN and total bilirubin > 2 × ULN	4 (3.1%)	4 (2.6%)	18 (4.0%)

ALT = alanine transaminase; AST = aspartate transaminase; B-NHL = B-cell non-Hodgkin lymphoma; ESC = Escalation; EXP = Expansion; FL = follicular lymphoma; ISS = Integrated Summary of Safety; R/R = relapsed or refractory; ULN = upper limit of normal
Note: Percentages calculated based on N.
Source: ISS Table 6.5

Immunogenicity

Anti-drug antibody (ADA) was measured using different assays in Studies GCT3013-01 and GCT3013-04; therefore, pooled analysis is not possible to perform.

In the Study GCT3013-01 (ESC+EXP) R/R FL cohort, of the 120 immunogenicity-evaluable subjects treated with the 48-mg full dose of epcoritamab, on-treatment ADA status was positive for 3 (2.5%) subjects. Among these 3 subjects, 1 subject was transiently ADA-positive at C1D22 and was ADA negative for all other time points; 1 subject was transiently ADA-positive at C2D1 and was ADA negative for all other time points; 1 subject was transiently ADA-positive at C3D1 and was negative for all other time points. Of the 3 subjects with on-treatment positive ADAs, none had titer ≥ 1. Of the 3 subjects with R/R FL who were ADA positive on treatment (but not at baseline), one subject discontinued treatment due to disease progression after 3 cycles of treatment, and one was discontinued by the investigator due to recurrent infection, lack of patient compliance, and obtained complete remission after 4 cycles of treatment. The other subject had a best overall response of complete response as assessed by an Independent Review Committee and remained on treatment for more than 30 cycles after testing ADA positive. In addition, according to the MAH no notable safety issues were observed in the subjects.

In the Study GCT3013-04 (ESC+EXP) R/R FL cohort, of the 21 immunogenicity-evaluable subjects treated with the 48-mg full dose of epcoritamab, on-treatment ADA status was positive for 1 subject with a maximum titer value of 2, who was ADA negative at baseline. This subject was transiently ADA-positive from C1D22 through C2D1, then was ADA-negative for all subsequent time points.

The 1 R/R FL subject who was ADA positive on treatment (but not at baseline) in the Expansion Part of Study GCT3013-04 achieved a best overall response of complete response at Week 6 and maintained complete response until discontinuation on D526 due to an AE of progressive multifocal leukoencephalopathy.

Of 71 immunogenicity-evaluable subjects in Arm A of the FL optimization cohort of study GCT3013-01, where the new 3-step SUD was employed, on-treatment ADA status was positive for 5 (7.0%) subjects. None of the positive evaluations had titer ≥1.

The MAH stated that 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.

Vital signs

Pooled analyses were not performed for vital signs. In the GCT3013-01 Expansion Part iNHL cohort the most common clinically notable vital sign findings in subjects with FL were elevated temperature (82 [64.1%] subjects), diastolic blood pressure below normal (37 [28.9%] subjects), and systolic blood pressure below normal (31 [24.2%] subjects).

Overall, 5 (4.0%) subjects with FL had on-treatment abnormal, clinically significant changes in ECG, and 82 (65.6%) subjects with FL had abnormal, not clinically significant changes in ECG. At baseline, 5 (3.9%) subjects with FL had QTcF interval > 450 to 480 msec, and no subject with FL had QTcF interval > 480 msec. During the treatment period, QTcF interval >450 to 480 msec was observed in 18 (21.2%) subjects with FL, QTcF interval >480 to 500 msec was observed in 2 (2.4%) subjects with FL, and QTcF interval >500 msec was observed in 6 (7.1%) subjects with FL and also in 2 subjects with other subtypes.

The episodes of QTc >500 msec were usually single events, and the QTc returned to baseline later on study. For 3 subjects low grade electrolyte abnormalities (hypocalcaemia and/or hypokalaemia) reported. One event was reported as a Grade 3 AE of ECG QT prolonged, which was considered to be unrelated to epcoritamab; this subject had concurrent Grade 2 hypocalcaemia and Grade 2 hypokalaemia, both of which required treatment. For all subjects with QTc >500 msec, at least one of the following risk-factors were present: 1) relevant prior or ongoing cardiac disease/conditions, 2)

relevant concomitant medications which could affect QTc interval, or 3) had long QTc intervals already present at baseline of the study.

In the GCT3013-01 study the following findings were reported:

For the aNHL Cohort, post baseline QTcF intervals >480 to 500 msec and >500 msec were reported in 5 (5.0%) subjects and 5 (5.0%) subjects overall, respectively. Of the 5 subjects with QTcF >500 msec, 1 subject was reported with an AE of long QT syndrome, which was not considered related to epcoritamab, but attributed to a pre-existing condition requiring pacemaker insertion. The other 4 subjects had abnormalities that were not considered clinically meaningful and were not reported as AEs.

For the MCL cohort, on-treatment abnormal, clinically significant ECG changes were observed in 5 (8.3%) subjects, and abnormal but not clinically significant changes were observed in 41 (68.3%) subjects. A QTcF interval >480 to 500 ms was observed in 1 (2.6%) subject and QTcF interval >500 ms was observed in 4 (10.5%) subjects, but no AE were reported. The events were associated with high baseline QTc or relevant cardiac history or ongoing conditions.

Safety in special populations

Age

The incidences of higher grade TEAEs (≥ Grade 3), serious TEAEs, and TEAEs leading to treatment discontinuation generally increase as the age group shifts toward more elderly subjects (Table 47). This trend was observed in all safety pools. This trend was also observed with serious CRS, serious infections, cytopenia and febrile neutropenia.

Table 47: Overview of Treatment-Emergent Adverse Events by Age

	GCT3013-01 ESC+EXP R/R FL		
	<65 years (N=62)	65-<75 years (N=50)	>=75 years (N=17)
Number of subjects with at least one TEAE	60 (96.8%)	50 (100%)	17 (100%)
Drug-related TEAE	56 (90.3%)	47 (94.0%)	17 (100%)
Grade 3 and higher TEAE	37 (59.7%)	38 (76.0%)	14 (82.4%)
Grade 3 and higher drug-related TEAE	22 (35.5%)	19 (38.0%)	7 (41.2%)
Grade 3 or 4 TEAE	36 (58.1%)	35 (70.0%)	13 (76.5%)
Grade 3 or 4 drug-related TEAE	22 (35.5%)	19 (38.0%)	7 (41.2%)
TEAE by worst toxicity grade			
1	5 (8.1%)	1 (2.0%)	1 (5.9%)
2	18 (29.0%)	11 (22.0%)	2 (11.8%)
3	25 (40.3%)	19 (38.0%)	7 (41.2%)
4	11 (17.7%)	11 (22.0%)	3 (17.6%)
5	1 (1.6%)	8 (16.0%)	4 (23.5%)
Serious TEAE	39 (62.9%)	36 (72.0%)	14 (82.4%)
Serious drug-related TEAE	23 (37.1%)	26 (52.0%)	11 (64.7%)
TEAE leading to treatment discontinuation	6 (9.7%)	12 (24.0%)	6 (35.3%)
Drug-related TEAE leading to treatment discontinuation	1 (1.6%)	3 (6.0%)	1 (5.9%)

Note: Percentages calculated based on N.
Note: Adverse events are classified using MedDRA v26.0 and CTCAE v5.0, and are counted only once per category. CRS and ICANS are graded according to ASTCT criteria (Lee et al., 2019) and CTLS by Cairo-Bishop criteria (Coiffier et al., 2008).
[a] Includes TEAEs with action taken of dose delay or dose interruption.

Comparison of safety in different age groups is shown in

Table **48**. Of note, no age-related trends in the frequency and severity of events across other TEAE categories and the AESIs of ICANS and CTLS are observed. Any Grade CRS is observed in respectively 66.1%, 66.0% and 70.6% in age subgroups of <65 years; 65-<75 years and >=75 years.

Table 48: Selected Treatment-Emergent Adverse Events by Age Group (48 mg Dose -- GCT3013-01 ESC+EXP–R/R FL)

	GCT3013-01 ESC+EXP R/R FL (N=129)		
MedDRA Terms	**Age <65 (N=62)**	**Age 65-74 (N=50)**	**Age 75-84 (N=17)**
Total AEs	61 (98.4%)	50 (100%)	17 (100%)
Serious AEs – Total	40 (64.5%)	36 (72.0%)	15 (88.2%)
Fatal	1 (1.6%)	8 (16.0%)	5 (29.4%)
Hospitalization/prolong existing hospitalization	39 (62.9%)	35 (70.0%)	14 (82.4%)
Life-threatening	1 (1.6%)	3 (6.0%)	4 (23.5%)
Disability/incapacity	2 (3.2%)	1 (2.0%)	1 (5.9%)
Other (medically significant)	7 (11.3%)	5 (10.0%)	2 (11.8%)
AE leading to drop-out	7 (11.3%)	13 (26.0%)	8 (47.1%)
Psychiatric disorders	13 (21.0%)	11 (22.0%)	7 (41.2%)
Nervous system disorders	27 (43.5%)	29 (58.0%)	5 (29.4%)
Accidents and injuries	2 (3.2%)	9 (18.0%)	4 (23.5%)
Cardiac disorders	5 (8.1%)	9 (18.0%)	4 (23.5%)
Vascular disorders	5 (8.1%)	8 (16.0%)	3 (17.6%)
Cerebrovascular disorders	0	0	0
Infections and infestations	47 (75.8%)	39 (78.0%)	15 (88.2%)
Anticholinergic syndrome	0	0	0
Quality of life decreased	0	0	0
Any postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	7 (11.3%)	11 (22.0%)	5 (29.4%)
Other AEs appearing more frequently in older subjects:			
Abdominal pain upper	4 (6.5%)	4 (8.0%)	2 (11.8%)
Acute kidney injury	2 (3.2%)	1 (2.0%)	3 (17.6%)
Anaemia	7 (11.3%)	9 (18.0%)	4 (23.5%)
Asthenia	6 (9.7%)	4 (8.0%)	2 (11.8%)
Atrial fibrillation	1 (1.6%)	2 (4.0%)	2 (11.8%)
Back pain	8 (12.9%)	7 (14.0%)	3 (17.6%)
Blood creatinine increased	2 (3.2%)	4 (8.0%)	3 (17.6%)
COVID-19 pneumonia	3 (4.8%)	6 (12.0%)	4 (23.5%)
Constipation	8 (12.9%)	7 (14.0%)	5 (29.4%)
Cough	11 (17.7%)	11 (22.0%)	3 (17.6%)
Cytokine release syndrome	41 (66.1%)	33 (66.0%)	12(70.6%)
Decreased appetite	4 (6.5%)	4 (8.0%)	4 (23.5%)
Diarrhoea	16 (25.8%)	15 (30.0%)	5 (29.4%)
Dizziness	6 (9.7%)	6 (12.0%)	3 (17.6%)
Dry skin	4 (6.5%)	1 (2.0%)	3 (17.6%)
Dyspnoea	7 (11.3%)	7 (14.0%)	4 (23.5%)
Fatigue	17 (27.4%)	19 (38.0%)	7 (41.2%)
Hyperhidrosis	4 (6.5%)	4 (8.0%)	2 (11.8%)
Injection site reaction	20 (32.3%)	22 (44.0%)	5 (29.4%)
Insomnia	6 (9.7%)	9 (18.0%)	3 (17.6%)
Lymphocyte count decreased	4 (6.5%)	2 (4.0%)	2 (11.8%)
Lymphopenia	2 (3.2%)	6 (12.0%)	2 (11.8%)
Muscular weakness	0	2 (4.0%)	2 (11.8%)
Nasopharyngitis	1 (1.6%)	6 (12.0%)	2 (11.8%)
Neutropenia	15 (24.2%)	8 (16.0%)	4 (23.5%)
Neutrophil count decreased	5 (8.1%)	6 (12.0%)	2 (11.8%)
Night sweats	0	2 (4.0%)	3 (17.6%)
Oedema peripheral	5 (8.1%)	6 (12.0%)	7 (41.2%)
Palmar-plantar erythrodysaesthesia syndrome	1 (1.6%)	1 (2.0%)	2 (11.8%)
Pneumonia	2 (3.2%)	6 (12.0%)	2 (11.8%)
Pollakiuria	1 (1.6%)	1 (2.0%)	2 (11.8%)

Pruritus	6 (9.7%)	4 (8.0%)	3 (17.6%)
Pyrexia	17 (27.4%)	10 (20.0%)	5 (29.4%)
Rash	4 (6.5%)	5 (10.0%)	2 (11.8%)
Respiratory tract infection	1 (1.6%)	1 (2.0%)	2 (11.8%)
Skin infection	0	1 (2.0%)	2 (11.8%)
Skin laceration	0	3 (6.0%)	2 (11.8%)
Stomatitis	2 (3.2%)	2 (4.0%)	2 (11.8%)
Upper respiratory tract infection	6 (9.7%)	7 (14.0%)	5 (29.4%)
Urinary tract infection	4 (6.5%)	7 (14.0%)	2 (11.8%)

Note: Percentages calculated based on N.

Note: Adverse events are classified using MedDRA v26.1 and are counted only once per system organ class and only once per preferred term.

Note: The data in this table are provided to satisfy the CHMP Rapporteur's request in the Request for Supplementary Information to complete Table 45 "Comparison of safety in different age groups."

Data cutoff date: 16 October 2023

Source: Table q25

Sex

In general, the frequency and severity of events were similar between female and male subjects across most TEAE categories and the AESIs, with the following exceptions showing differences in incidence ≥ 10% between female and male subjects, respectively:

- Drug-related serious TEAE: 34.7% vs 53.8%
- Grade 3 or higher drug-related TEAEs: 28.6% vs 42.5%
- Grade 5 TEAEs (fatal TEAEs): 16.3% vs 6.3%
- TEAE leading to treatment discontinuation: 30.6% vs 11.3%
- Drug-related TEAE leading to dose delay: 28.6% vs 38.8%
- CRS of all grades: 57.1% vs 72.5%
- Serious CRS: 30.6% vs 48.8%
- CRS leading to dose delay: 4.1% vs 16.3%
- Serious infections: 32.7% vs 45.0%
- Grade 3 or higher serious infections: 28.6% vs 41.3%
- Serious infection TEAEs leading to dose delay: 16.3% vs 30.0%

In Safety Pool 01+04 R/R FL, TEAEs by sex subgroup were similar to that described above for Safety Pool 01 R/R FL (ISS Table 4.6). In Safety Pool 01+04 All B NHL, there were no apparent sex-related trends in the frequency and severity of events across TEAE and AESI categories.

Race

In Safety Pool 01+04 R/R FL, the frequency and severity of events were similar between race subgroups across TEAE categories and the AESIs with the following exceptions showing differences in incidence ≥ 10% among the White (N=77), Asian (N=29), and Other (N=45) race subgroups:

- Grade 3 or higher drug-related TEAEs was highest in Asian (55.2%), followed by White (39.0%) and Other race subgroup (33.3%).

- Serious TEAEs: was highest in Other race subgroup (86.7%), followed by White (61.0%) and Asian (51.7%).
- Drug-related serious TEAEs was highest in Other (60.0%), followed by Asian (44.8%) and White (40.3%).
- CRS (all grades) was highest in Asian (82.8%), followed by Other (71.1%) and White (63.6%).
- Serious CRS was highest in Other (51.1%), followed by White (37.7%) and Asian (24.1%)

The higher incidence of any grade CRS in the Asian subgroup in Safety Pool 01+04 R/R FL (82.8%) compared with that in Safety Pool 01 R/R FL (71.4%) was driven by the smaller GCT3013-04 study, which had an incidence of any grade CRS of 90.5% in the FL subjects.

Additionally, the incidence of all-grade CRS was the highest in Asian across the race subgroups, yet the incidence of serious CRS was the lowest in Asian subgroup. Exposure-safety analyses suggest that there was no apparent relationship between PK and CRS (any grade or Grade 2 or higher). Therefore, the exposure-safety modelling data may indicate that the higher incidence of CRS in the Asian subgroup from Safety Pool 01+04 R/R FL is not either epcoritamab-related or due to higher exposures to epcoritamab in Asian subjects, but rather due to other unidentified confounding factors.

In Safety Pool 01+04 All B-NHL, similar trends were observed in CRS events and neurological events (broad definition) as those stated for Safety Pool 01+04 R/R FL.

Baseline renal function

In general, the frequency and severity of events were similar across TEAE and AESI categories. In Safety Pool 01 R/R FL, consistent trends were observed with worsening baseline renal function with differences in incidence ≥ 10% between the highest and lower rates among the normal (N=53) , mildly impaired (n=54), and moderately impaired (n=22) renal function subgroups, respectively, in the following:

- Fatal TEAEs: 3.8% vs 11.1% vs 22.7%
- TEAEs leading to treatment discontinuation: 7.5% vs 25.9% vs 27.3%

In Safety Pool 01+04 R/R FL and Safety Pool 01+04 All B-NHL, there were no consistent trends observed in TEAEs by baseline renal function subgroup.

Table 49: Overview of Treatment-Emergent Adverse Events by Baseline Renal Function

	GCT3013-01 ESC+EXP		
	R/R FL		
	Normal (>=90) (N=53)	Mildly Impaired (60 - <90) (N=54)	Moderately Impaired (30 - <60) (N=22)
Number of subjects with at least one TEAE	52 (98.1%)	53 (98.1%)	22 (100%)
Drug-related TEAE	48 (90.6%)	53 (98.1%)	19 (86.4%)
Grade 3 and higher TEAE	31 (58.5%)	42 (77.8%)	16 (72.7%)
Grade 3 and higher drug-related TEAE	15 (28.3%)	27 (50.0%)	6 (27.3%)
Grade 3 or 4 TEAE	30 (56.6%)	41 (75.9%)	13 (59.1%)
Grade 3 or 4 drug-related TEAE	15 (28.3%)	27 (50.0%)	6 (27.3%)
TEAE by worst toxicity grade			
1	4 (7.5%)	2 (3.7%)	1 (4.5%)
2	17 (32.1%)	9 (16.7%)	5 (22.7%)
3	23 (43.4%)	22 (40.7%)	6 (27.3%)
4	6 (11.3%)	14 (25.9%)	5 (22.7%)
5	2 (3.8%)	6 (11.1%)	5 (22.7%)
Serious TEAE	34 (64.2%)	42 (77.8%)	13 (59.1%)
Serious drug-related TEAE	22 (41.5%)	28 (51.9%)	10 (45.5%)
TEAE leading to treatment discontinuation	4 (7.5%)	14 (25.9%)	6 (27.3%)
Drug-related TEAE leading to treatment discontinuation	0	3 (5.6%)	2 (9.1%)
TEAE leading to dose delay [a]	32 (60.4%)	33 (61.1%)	12 (54.5%)
Drug-related TEAE leading to dose delay [a]	17 (32.1%)	21 (38.9%)	7 (31.8%)
Fatal TEAE	2 (3.8%)	6 (11.1%)	5 (22.7%)
Fatal drug-related TEAE	0	0	0

	GCT3013-01 ESC+EXP and GCT3013-04 ESC+EXP					
	R/R FL			All B-NHL		
	Normal (>=90) (N=56)	Mildly Impaired (60 - <90) (N=65)	Moderately Impaired (30 - <60) (N=30)	Normal (>=90) (N=167)	Mildly Impaired (60 - <90) (N=193)	Moderately Impaired (30 - <60) (N=89)
Number of subjects with at least one TEAE	55 (98.2%)	64 (98.5%)	30 (100%)	166 (99.4%)	189 (97.9%)	89 (100%)
Drug-related TEAE	51 (91.1%)	64 (98.5%)	27 (90.0%)	145 (86.8%)	178 (92.2%)	83 (93.3%)
Grade 3 and higher TEAE	33 (58.9%)	52 (80.0%)	20 (66.7%)	119 (71.3%)	150 (77.7%)	64 (71.9%)
Grade 3 and higher drug-related TEAE	17 (30.4%)	35 (53.8%)	9 (30.0%)	68 (40.7%)	99 (51.3%)	39 (43.8%)
Grade 3 or 4 TEAE	32 (57.1%)	51 (78.5%)	17 (56.7%)	116 (69.5%)	146 (75.6%)	59 (66.3%)
Grade 3 or 4 drug-related TEAE	17 (30.4%)	35 (53.8%)	9 (30.0%)	68 (40.7%)	98 (50.8%)	36 (40.4%)
TEAE by worst toxicity grade						
1	4 (7.1%)	3 (4.6%)	2 (6.7%)	10 (6.0%)	10 (5.2%)	4 (4.5%)
2	18 (32.1%)	9 (13.8%)	8 (26.7%)	37 (22.2%)	29 (15.0%)	21 (23.6%)
3	25 (44.6%)	28 (43.1%)	8 (26.7%)	71 (42.5%)	72 (37.3%)	31 (34.8%)
4	6 (10.7%)	18 (27.7%)	7 (23.3%)	38 (22.8%)	54 (28.0%)	21 (23.6%)
5	2 (3.6%)	6 (9.2%)	5 (16.7%)	10 (6.0%)	24 (12.4%)	12 (13.5%)
Serious TEAE	36 (64.3%)	49 (75.4%)	16 (53.3%)	108 (64.7%)	135 (69.9%)	57 (64.0%)
Serious drug-related TEAE	24 (42.9%)	35 (53.8%)	12 (40.0%)	69 (41.3%)	89 (46.1%)	40 (44.9%)
TEAE leading to treatment discontinuation	4 (7.1%)	16 (24.6%)	8 (26.7%)	20 (12.0%)	36 (18.7%)	20 (22.5%)
Drug-related TEAE leading to treatment discontinuation	0	5 (7.7%)	2 (6.7%)	4 (2.4%)	8 (4.1%)	7 (7.9%)
TEAE leading to dose delay [a]	34 (60.7%)	39 (60.0%)	14 (46.7%)	86 (51.5%)	103 (53.4%)	47 (52.8%)
Drug-related TEAE leading to dose delay [a]	18 (32.1%)	25 (38.5%)	9 (30.0%)	46 (27.5%)	61 (31.6%)	29 (32.6%)
Fatal TEAE	2 (3.6%)	6 (9.2%)	5 (16.7%)	10 (6.0%)	25 (13.0%)	12 (13.5%)
Fatal drug-related TEAE	0	0	0	0	2 (1.0%)	4 (4.5%)

Note: Percentages calculated based on N.
Note: Adverse events are classified using MedDRA v26.0 and CTCAE v5.0, and are counted only once per category. CRS and ICANS are graded according to ASTCT criteria (Lee et al., 2019) and CTLS by Cairo-Bishop criteria (Coiffier et al., 2008).
[a] Includes TEAEs with action taken of dose delay or dose interruption.

Program Source Code: /SDA/EPCO/FL/SUBMISSION2023/ISS/2.4/PCMS_RUN/iss-ovae-sub.sas

Baseline hepatic function

In Safety Pool 01 R/R FL trends were observed of lower incidences across TEAE categories and the AESIs of CRS and ICANS in the normal group (N=108) compared with the mild hepatic dysfunction (N=21) group, respectively, with differences ≥ 10% between subgroups noted below:

- Serious TEAEs: 64.8% vs 90.5%
- Drug-related serious TEAEs: 44.4% vs 57.1%
- Grade 3 or 4 TEAE: 63.0% vs 76.2%
- Serious CRS: 38.9% vs 57.1%
- Neurological events (broad definition): 46.3% vs 57.1%

- Serious infections: 37.0% vs 57.1%
- Drug-related serious infections: 7.4% vs 19.0%
- Grade 3 or 4 serious infections: 29.6% vs 42.9%
- Cytopenia (broad): 43.5% vs 61.9%
- Grade 3 or 4 cytopenia (broad): 33.3% vs 57.1%
- Injection site reactions: 54.6% vs 66.7%

In Safety Pool 01+04 R/R FL, TEAEs by baseline hepatic function subgroups were similar to that described above for Safety Pool 01 R/R FL whereas in Safety Pool 01+04 All B-NHL differences in Grade 3 or 4 TEAE (69.8% versus 79.7%) and in serious TEAE (64.2% versus 78.4%) were observed and other differences were not so outspoken as in the Safety Pool 01 R/R FL.

Double refractory to anti-CD20 and alkylating Agent

In Safety Pool 01 R/R FL, lower incidences (by ≥ 10%) of the following TEAEs and AESIs were observed in the double refractory to anti-CD20 and alkylating agent subgroup compared with the not double refractory subgroup:

- Grade 3 or 4 TEAEs: 61.5% vs 73.7%
- Drug-related Grade 3 or 4 TEAEs: 29.7% vs 55.3%
- Serious TEAEs: 64.8% vs 78.9%
- Drug-related serious TEAEs: 41.8% vs 57.9%
- TEAEs leading to treatment discontinuation: 15.4% vs 26.3%
- CRS: 59.3% vs 84.2%
- Serious CRS: 36.3% vs 55.3%
- Neurological events (broad definition): 40.7% vs 65.8%
- Drug-related neurological events (broad definition): 17.6% vs 28.9%
- Serious infections: 37.4% vs 47.4%
- Cytopenia (broad): 40.7% vs 60.5%
- Grade 3 or 4 cytopenia (broad): 31.9% vs 50.0%
- Neutropenia (grouped): 19.8% vs 47.4%
- Drug-related neutropenia (grouped): 17.6% vs 42.1%
- Grade 3 or 4 neutropenia (grouped): 16.5% vs 44.7%
- Drug-related Grade 3 or 4 neutropenia (grouped): 14.3% vs 39.5%

In Safety Pool 01+04 R/R FL, the frequency and severity of TEAEs and various AESI categories were similar to that reported in Safety Pool 01 R/R FL (ISS Table 4.56.1 and ISS Table 4.60.1). Safety Pool 01+04 All B-NHL is not discussed as double-refractory to anti-CD20 and alkylating agent is indication-specific.

Other

Subgroups based on baseline weight, region, prior lines of anti-lymphoma therapy/status, prior CAR-T cell therapy, Ann Arbor staging, double refractory to anti-cD20 and alkylating agent status have also been provided in the CSR, however are not reflected here.

Use in pregnancy and lactation

No clinical data is available regarding use of epcoritamab during human pregnancy or lactation.

Safety related to drug-drug interactions and other interactions

Epcoritamab causes the release of cytokines that may suppress activity of cytochrome P450 (CYP) enzymes, resulting in increased exposure of CYP substrates. Increased exposure of CYP substrates is more likely to occur after the first dose of epcoritamab on Cycle 1 Day 1 and up to 14 days after the first 48 mg dose, and during and after CRS. The 3-step SUD regimen (0.16/0.8/3/48 mg) along with adequate hydration and use of dexamethasone further reduced the release of cytokines, and therefore potentially the risk of drug interactions.

No new drug-drug interactions have been identified.

Discontinuation due to adverse events

In Safety Pool 01 R/R FL (N=129), TEAEs leading to treatment discontinuation were reported for 18.6% of subjects. TEAEs leading to treatment discontinuation reported in more than 2% of subjects (2 subjects) included COVID-19 pneumonia (5.4%) and COVID-19 (3.9%). A total of 5 (3.9%) subjects experienced TEAEs leading to discontinuation that were considered drug-related by the investigator, including 4 subjects who discontinued treatment due to drug-related TEAEs of COVID-19 (Grade 2), enteritis (Grade 3), pneumonitis (Grade 3), and diarrhea (Grade 1) (reported in 1 subject each); the remaining subject had 2 drug-related TEAEs that led to treatment discontinuation (fatigue and malaise, both were Grade 2).

Table 50: Treatment-Emergent Adverse Events Leading to Treatment Discontinuation by SOC and PT

System Organ Class Preferred Term	GCT3013-01 ESC+EXP R/R FL (N=129)	GCT3013-01 ESC+EXP and GCT3013-04 ESC+EXP R/R FL (N=151)	 All B-NHL (N=449)
Subjects with at least one TEAE leading to treatment discontinuation	24 (18.6%)	28 (18.5%)	76 (16.9%)
Infections and infestations	17 (13.2%)	19 (12.6%)	47 (10.5%)
COVID-19 pneumonia	7 (5.4%)	7 (4.6%)	22 (4.9%)
COVID-19	5 (3.9%)	5 (3.3%)	13 (2.9%)
Hepatitis E	2 (1.6%)	2 (1.3%)	2 (0.4%)
Pneumonia	1 (0.8%)	1 (0.7%)	2 (0.4%)
Pseudomonal sepsis	1 (0.8%)	1 (0.7%)	1 (0.2%)
Sinusitis	1 (0.8%)	1 (0.7%)	1 (0.2%)
Pneumonia bacterial	0	0	1 (0.2%)
Progressive multifocal leukoencephalopathy	0	2 (1.3%)	3 (0.7%)
Pseudomonal bacteraemia	0	0	1 (0.2%)
Septic shock	0	0	2 (0.4%)
Gastrointestinal disorders	2 (1.6%)	2 (1.3%)	2 (0.4%)
Diarrhoea	1 (0.8%)	1 (0.7%)	1 (0.2%)
Enteritis	1 (0.8%)	1 (0.7%)	1 (0.2%)
General disorders and administration site conditions	2 (1.6%)	3 (2.0%)	6 (1.3%)
Fatigue	1 (0.8%)	1 (0.7%)	2 (0.4%)
General physical health deterioration	1 (0.8%)	1 (0.7%)	2 (0.4%)
Malaise	1 (0.8%)	2 (1.3%)	2 (0.4%)
Multiple organ dysfunction syndrome	0	0	1 (0.2%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (1.6%)	3 (2.0%)	10 (2.2%)
Angioimmunoblastic T-cell lymphoma	1 (0.8%)	1 (0.7%)	1 (0.2%)
Malignant peritoneal neoplasm	1 (0.8%)	1 (0.7%)	1 (0.2%)
Anogenital warts	0	0	1 (0.2%)
Chronic myelomonocytic leukaemia	0	0	1 (0.2%)
Lung neoplasm malignant	0	0	2 (0.4%)
Myelodysplastic syndrome	0	0	2 (0.4%)
Pancreatic carcinoma	0	0	1 (0.2%)
Prostate cancer	0	1 (0.7%)	1 (0.2%)
Respiratory, thoracic and mediastinal disorders	2 (1.6%)	2 (1.3%)	2 (0.4%)
Interstitial lung disease	1 (0.8%)	1 (0.7%)	1 (0.2%)
Pneumonitis	1 (0.8%)	1 (0.7%)	1 (0.2%)
Cardiac disorders	1 (0.8%)	1 (0.7%)	3 (0.7%)
Cardiopulmonary failure	1 (0.8%)	1 (0.7%)	1 (0.2%)
Myocardial infarction	0	0	1 (0.2%)
Myocarditis	0	0	1 (0.2%)
Ear and labyrinth disorders	0	0	1 (0.2%)
Deafness	0	0	1 (0.2%)
Immune system disorders	0	0	4 (0.9%)
Cytokine release syndrome	0	0	4 (0.9%)
Investigations	0	0	1 (0.2%)
Electrocardiogram QT prolonged	0	0	1 (0.2%)
Musculoskeletal and connective tissue disorders	0	0	1 (0.2%)
Muscular weakness	0	0	1 (0.2%)
Nervous system disorders	0	0	4 (0.9%)
Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids	0	0	1 (0.2%)

System Organ Class Preferred Term	GCT3013-01 ESC+EXP	GCT3013-01 ESC+EXP and GCT3013-04 ESC+EXP	
	R/R FL (N=129)	R/R FL (N=151)	All B-NHL (N=449)
Immune effector cell-associated neurotoxicity syndrome	0	0	2 (0.4%)
Peripheral sensory neuropathy	0	0	1 (0.2%)

B-NHL = B-cell non-Hodgkin lymphoma; COVID-19 = Coronavirus-Disease-2019; ESC = Escalation; EXP = Expansion; FL = follicular lymphoma; ISS = Integrated Summary of Safety; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; R/R = relapsed or refractory; SOC = System Organ Class; TEAE = treatment-emergent adverse event; v = version
Note: Percentages calculated based on N.
Adverse events are classified using MedDRA v26.0 and are counted only once per system organ class and only once per preferred term.
Source: ISS Table 3.20

GCT3013-01 optimization part step up dosing

Methods

Study GCT3013-01 includes an ongoing Optimization Part with a DLBCL, MCL and FL cohort. The FL cohort investigates an alternative 3 step SUD regimens along with adequate hydration and dexamethasone (15 mg) premedication in Cycle 1 to reduce the risk of ≥ Grade 2 CRS and all grade CRS; Table *51*). Further, extensive repriming instructions and dose modifications for CRS events were in place. In more detail, it was strongly recommended that all subjects adhere to the following fluid guidelines during Cycle 1, unless medically contraindicated:

- 2-3 L of fluid intake during the 24 hours prior to each epcoritamab administration.
- Hold antihypertensive medications for 24 hours prior to each epcoritamab administration.
- Administer 500 mL isotonic intravenous (IV) fluids on the day of epcoritamab prior to dose administration;
- AND 2-3 L of fluid intake during the 24 hours following each epcoritamab.

Repriming Instructions:

- A repriming cycle was required if the epcoritamab dose was delayed at certain timepoints:
- If an intermediate dose was delayed more than 1 day (i.e., > 8 days after priming or any intermediate dose)
- If the first full dose was delayed more than 7 days (i.e., > 14 days since the last intermediate dose)
- For the second full dose onward, if the interval between the previous dose of epcoritamab and next epcoritamab dose exceeded 6 weeks PA9 further specified that a repriming cycle is a repetition of the Cycle 1 SUD schedule (as assigned for each cohort). Administration of corticosteroids and hydration, as per PA9, was also required during the repriming cycle for all subjects.

Dose modifications:

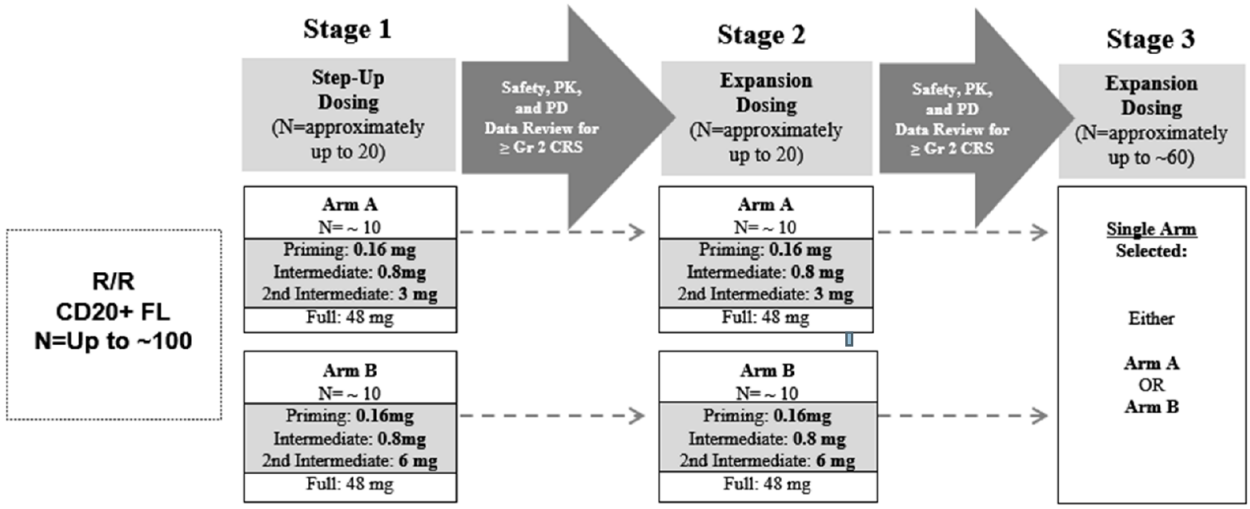
As of PA9, epcoritamab was required to be held until complete resolution of Grade ≤ 3 CRS and permanently discontinued for subjects with either Grade 4 CRS or any-grade CRS with concurrent macrophage activation syndrome/hemophagocytic lymphohistiocytosis (HLH).

The FL optimization cohort enrolled subjects with FL grades 1-3A and eligibility criteria are the same as for the R/R iNHL cohort expansion part. FL patients were included in parallel into 2 arms, both with an alternative 3-step SUD regimen (i.e., with an additional second intermediate dose); up to approximately 10 subjects were to be enrolled in each arm in Stage 1 (Figure 22). Of note, the DLBCL and MCL cohorts tested a different posology without a 2nd intermediated dose.

Hospitalization for the purpose of safety monitoring during or immediately following administration of the first full dose of epcoritamab was not required for subjects in this cohort, but was allowed per the investigator's discretion. Subjects who were not hospitalized were to remain in close proximity to the

treatment facility (within 30 minutes distance) for 24 hours after the first full dose of epcoritamab (i.e., C1D22).

Figure 20: Overview of Optimization Trial Design (FL Optimization Cohort)



Abbreviations: CRS = cytokine release syndrome; FL=follicular lymphoma; Gr2=grade 2; PD=pharmacodynamic; PK=pharmacokinetic; R/R=relapsed and/or refractory.

Table 51: Optimization Regimens for FL Grades 1-3A

	Priming Dose (Cycle 1 Day 1)	First Intermediate Dose (Cycle 1 Day 8)	Second Intermediate Dose (Cycle 1 Day 15)	First Full Dose (Cycle 1 Day 22)	Second Full Dose (Cycle 2 Day 1)
Arm A	0.16 mg	0.8 mg	3 mg	48 mg	48 mg
Arm B	0.16 mg	0.8 mg	6 mg	48 mg	48 mg

Abbreviations: EXP=Expansion; FL=follicular lymphoma, SUD=step-up dosing.

Subjects were premedicated with corticosteroids, antihistamines, and antipyretics 30 to 120 minutes prior to the first 4 doses of epcoritamab. Corticosteroid prophylaxis continued daily on Days 2, 3, and 4 after the first 4 doses of epcoritamab. For all subsequent doses of epcoritamab in Cycle 2 and beyond, premedication and CRS prophylaxis were optional. If CRS ≥ grade 2 occurred following the fourth epcoritamab administration (first full dose) on C1D22, 4-day consecutive corticosteroids were to be repeated for CRS prophylaxis with each epcoritamab dose until 1 full epcoritamab dose was administered without subsequent occurrence of CRS of any grade. During the first cycle (i.e., the first 4 administrations of epcoritamab), it was strongly recommended that subjects adhere to measures for sufficient fluid intake. The recommended corticosteroid for prophylaxis in the optimization cohort was dexamethasone.

The primary endpoint was rate of ≥ Grade 2 CRS events and all grade CRS events from first dose of epcoritamab through 7 days following administration of the second full dose of epcoritamab. Secondary endpoints were Rate of ≥ Grade 2 CRS events and all grade CRS events following first full dose; rate of ≥ Grade 2 CRS events and all grade CRS events overall; and safety.

In Stage 1: up to approximately 10 subjects will be enrolled into each of the dose levels being tested. Safety, PK, and pharmacodynamic data will be reviewed for these subjects on an ongoing basis to inform decision-making on early termination of one or more arms. The decision to terminate any arm

will be based on any safety concerns, including evidence indicating that the CRS profile for an alternative regimen may be worse than the current SUD regimen relative to reference Arm A.

Stage 2: based on ongoing review of the PK, pharmacodynamic, and safety data, additional subjects (up to approximately 10) may be added to at least one of the arms (at a particular dosing regimen).

Stage 3: a final expansion of up to approximately an additional 60 subjects each for in at least one arm may be implemented if a reduction in the rate of CRS ≥ Grade 2 is observed as compared to the rate observed for the corresponding cohort in the expansion part of the trial.

Based on the PK, pharmacodynamic, and safety data generated, additional modifications to the priming and/or intermediate doses may be proposed in order to further optimize epcoritamab dosing.

For FL grades 1-3A subjects, 2 arms will be enrolled in parallel, and will enrol up to approximately 10 subjects each. The dose optimization for FL grades 1-3A will assess 2 alternative second intermediate doses in parallel.

The decision rule based on CRS after Stage 1 is as follows:

- If ≤2 of 10 subjects experience CRS events of Grade ≥2, the SUD regimen will be considered acceptable for further evaluation.
- If ≥3 of 10 subjects experience CRS events of Grade ≥2, the SUD escalation will be terminated.

The final decision will be based on the totality of all available data. If needed, additional full dose (not exceeding 48 mg) regimen(s) can be explored for further optimization.

For the FL cohorts, a sample size of 80 subjects at the selected dose regimen would provide more than 80% power to detect an event with true event rate at 2% or higher (i.e., probability of observing at least 1 event is greater than 80%).

The primary analysis will be conducted approximately 9 months after the last patient's first dose for the iNHL and aNHL expansion cohorts, and approximately 6 months after the last patient's first dose for the MCL cohort. For the aNHL and iNHL cohorts, the primary subtype (FL grades 1-3A) will be analyzed first, and then the overall aNHL or iNHL population will be analyzed.

Results

The initiation date of the study was 17 Oct 2022. On 10 Mar 2023, after 6 subjects each were enrolled in Arms A and B, preliminary analysis revealed a numerically lower CRS rate in Arm A as compared to Arm B, which was supported by modelling. In addition, the simpler instructions for dose preparation for the 3 mg dose compared to the 6 mg dose, which requires the use of two 4 mg/0.8 mL vials, was taken into consideration, and further enrollment in Arm A was then prioritized in the FL Optimization cohort. Therefore, The MAH primarily presents and interpret the data in subjects in Arm A of the FL optimization cohort (hereafter referred to as Arm A).

Initially preliminary safety, efficacy, PK, and PD data were been provided for the first 30 subjects treated in Arm A of the GCT3013-01 FL optimization cohort (herein referred to as the FL optimization cohort), along with 6 subjects treated in Arm B (CSR, not shown in AR), using a clinical data cutoff date of 31 Jul 2023 and a PK data cutoff date of 7 Jul 2023. The 30 subjects in Arm A have a minimum of 2 cycles of follow-up (data not shown). As of the 08 Jan 2024 data cutoff date, a total of 112 subjects were enrolled and 92 subjects (86 subjects in Arm A and 6 subjects Arm B) received at least 1 dose of epcoritamab in the FL Optimization Part of the GCT3013-01 trial. Twenty subjects did not meet the eligibility criteria and were not administered epcoritamab. All 86 subjects treated in Arm A were included in the Full Analysis Set. In total 64 (74.4%) subjects continued to receive epcoritamab

treatment and 22 (25.6%) subjects discontinued treatment. Seventeen (19.8%) subjects discontinued treatment due to progressive disease and 3 (3.5%) subject discontinued treatment due to an AE (1 subject due to bronchopulmonary aspergillosis and 2 subjects due to pneumonitis). The median age in Arm A was 63.5 years (range: 33, 90). A total of 49 (57.0%) subjects were male and 64 (74.4%) subjects were White. In total 79 (91.9%) subjects had advanced stage (Ann Arbor Stage III [including IIIE and IIIS] or IV) disease, and 44 (451.2%) subjects had a FLIPI score ≥ 3. The median number of prior lines of systemic anti-lymphoma therapy was 2 (range: 2, 9). Forty-four (62.8%) subjects were double refractory to anti-CD20 and alkylating agent and 42 (48.8%) subjects had POD24.

As of the data cut-off date of 08 Jan 2024, the median duration of treatment in the FL optimization cohort was 3.8 months (range:0.26, 11.83), and the median RDI in Cycles 1 to 3 was 94.6% (range: 44, 102). As of the data cutoff date, 8 (9.3%) subjects in Arm A required epcoritamab repriming due to a dose delay.

AEs

All safety analyses were conducted using the SAF, unless otherwise noted. The SAF in the FL optimization cohort included 86 subjects in Arm A who received at least 1 dose of epcoritamab. As of the data cutoff date of 08 Jan 2024, the median duration of trial follow-up was 5.7 months (range: 0.4, 11.8) in Arm A.

An overview of safety is presented Table 52.

Table 52: Overview of Treatment-Emergent Adverse Events – GCT3013-01

	Arm A (N=86)	Arm B (N=6)
Number of subjects with ≥1		
TEAE	85 (98.8%)	6 (100%)
Related TEAE	78 (90.7%)	5 (83.3%)
Grade 3 and higher TEAE	46 (53.5%)	3 (50.0%)
Grade 3 and higher related TEAE	29 (33.7%)	2 (33.3%)
TEAE by worst toxicity grade		
1	11 (12.8%)	0
2	28 (32.6%)	3 (50.0%)
3	32 (37.2%)	2 (33.3%)
4	14 (16.3%)	1 (16.7%)
5	0	0
Serious TEAE	38 (44.2%)	4 (66.7%)
Serious related TEAE	31 (36.0%)	3 (50.0%)
TEAE leading to treatment discontinuation	3 (3.5%)	0
TEAE leading to dose delay	50 (58.1%)	4 (66.7%)
Fatal TEAE	0	0
Fatal related TEAE	0	0
AESI		
CRS	42 (48.8%)	3 (50.0%)
ICANS	0	0
CTLS	0	0

Abbreviations: AESI = adverse event of special interest; CRS = cytokine release syndrome; CTLS = clinical tumor lysis syndrome; FL = follicular lymphoma; ICANS = immune effector cell-associated neurotoxicity syndrome; TEAE = treatment-emergent adverse event.
Arm A: Priming 0.16 mg, First Intermediate 0.8 mg, Second Intermediate 3 mg.
Arm B: Priming 0.16 mg, First Intermediate 0.8 mg, Second Intermediate 6 mg.
Note: Percentages calculated based on number of subjects in Safety Analysis Set. Adverse events are classified using Medical Dictionary for Regulatory Activities v26.1 and National Cancer Institute-Common Terminology Criteria for Adverse Events v5.0 and are counted only once per category. ICANS and CRS are graded according to (Lee et al., 2019) and CTLS according to Cairo-Bishop (Coiffier et al., 2008).
Data cutoff date: 08 Jan 2024
Source: Table 14.3.1.1.1

The most common (≥20%) TEAEs by PT were CRS (42 subjects; 48.8%), injection site reaction (23 subjects; 26.7%), and constipation (18 subjects; 20.9%; Table 53). The most frequent treatment-related TEAEs (in ≥10% of subjects) were CRS in 42 (48.8%) subjects, injection site reaction in 23 (26.7%) subjects, fatigue and neutropenia in 12 (14.0%) subjects each.

The Grade 3 or 4 TEAE PTs that occurred in more than 1 subject each were neutropenia (14 subjects; 16.3%), lymphocyte count decreased (6 subjects; 7.0%), lymphopenia and COVID-19 (4 subjects each; 4.7%), neutrophil count decreased (3 subjects; 3.5%), and anemia, thrombocytopenia, ALT increased, hyperglycemia, and hypokalemia (2 subjects each; 2.3%).

The most frequently reported serious TEAEs were CRS (24 subjects; 27.9%), COVID-19 (4 subjects; 4.7%), and COVID-19 pneumonia and urinary tract infection (2 subjects each; 2.3%). All other serious TEAEs occurred in 1 subject each. Of the 24 subjects with serious TEAEs of CRS, 17 (19.8%) subjects had grade 1 CRS events and 7 (8.1%) subjects had grade 2 CRS events.

Table 53: Most Common (≥10% in Arm A) Treatment-Emergent Adverse Events by SOC and PT – GCT3013-01 Optimization Part – FL 1-3A Cohort (Safety Analysis Set)

	Arm A (N=86)		Arm B (N=6)	
System Organ Class Preferred Term	All	Related	All	Related
Subjects with ≥1 TEAE	**85 (98.8%)**	**78 (90.7%)**	**6 (100%)**	**5 (83.3%)**
General disorders and administration site conditions	**53 (61.6%)**	**39 (45.3%)**	**5 (83.3%)**	**3 (50.0%)**
Injection site reaction	23 (26.7%)	23 (26.7%)	0	0
Fatigue	17 (19.8%)	12 (14.0%)	1 (16.7%)	0
Oedema peripheral	12 (14.0%)	2 (2.3%)	0	0
Pyrexia	12 (14.0%)	4 (4.7%)	0	0
Infections and infestations	**48 (55.8%)**	**28 (32.6%)**	**6 (100%)**	**1 (16.7%)**
COVID-19	16 (18.6%)	6 (7.0%)	2 (33.3%)	0
Gastrointestinal disorders	**47 (54.7%)**	**10 (11.6%)**	**4 (66.7%)**	**2 (33.3%)**
Constipation	18 (20.9%)	3 (3.5%)	1 (16.7%)	0
Diarrhoea	10 (11.6%)	2 (2.3%)	2 (33.3%)	1 (16.7%)
Nausea	11 (12.8%)	5 (5.8%)	1 (16.7%)	1 (16.7%)
Abdominal pain	9 (10.5%)	0	1 (16.7%)	0
Immune system disorders	**43 (50.0%)**	**43 (50.0%)**	**4 (66.7%)**	**3 (50.0%)**
Cytokine release syndrome	42 (48.8%)	42 (48.8%)	3 (50.0%)	3 (50.0%)
Respiratory, thoracic and mediastinal disorders	**33 (38.4%)**	**5 (5.8%)**	**2 (33.3%)**	**0**
Cough	14 (16.3%)	0	0	0
Blood and lymphatic system disorders	**29 (33.7%)**	**21 (24.4%)**	**1 (16.7%)**	**1 (16.7%)**
Neutropenia	15 (17.4%)	12 (14.0%)	1 (16.7%)	1 (16.7%)
Anaemia	10 (11.6%)	5 (5.8%)	1 (16.7%)	1 (16.7%)
Nervous system disorders	**24 (27.9%)**	**9 (10.5%)**	**1 (16.7%)**	**1 (16.7%)**
Headache	12 (14.0%)	6 (7.0%)	1 (16.7%)	1 (16.7%)
Musculoskeletal and connective tissue disorders	**22 (25.6%)**	**5 (5.8%)**	**3 (50.0%)**	**1 (16.7%)**
Arthralgia	11 (12.8%)	2 (2.3%)	1 (16.7%)	1 (16.7%)
Psychiatric disorders	**15 (17.4%)**	**1 (1.2%)**	**2 (33.3%)**	**0**
Insomnia	9 (10.5%)	0	0	0

Abbreviations: COVID-19 = coronavirus disease 2019; FL = follicular lymphoma; PT = preferred term; SOC = system organ class; TEAE = treatment-emergent adverse event.

No fatal TEAEs were observed. One (1.2%) subject in Arm A died due to disease progression on Day 41, 19 days after the last dose of epcoritamab, and 1 (16.7%) subject in Arm B died due to disease progression on Day 174, 74 days after the last dose of epcoritamab.

The three (3.5%) TEAEs leading to treatment discontinuation were bronchopulmonary aspergillosis in 1 subject and pneumonitis in 2 subjects (all events were considered related to epcoritamab). The most common TEAEs (≥10%) by PT leading to dose delay were CRS (16 subjects; 18.6%) and COVID-19 (15 subjects; 17.4%).

CRS

Of the 86 subjects treated with epcoritamab in the FL optimization cohort, 42 (48.8%) had at least 1 CRS event with the 3-step SUD regimen. In comparison, 86 (66.7%) subjects in Safety Pool 01 R/R FL had at least 1 CRS event with the 2-step-up dosing regimen.

Table 54: Subject-Level Summary of AESI: Cytokine Release Syndrome – GCT3013-01 Optimization Part – FL 1-3A Cohort (Safety Analysis Set)

Number of Subjects (%)	Arm A (N=86)	Arm B (N=6)
Subjects with ≥1 CRS event	**42 (48.8%)**	**3 (50.0%)**
Grade 1	34 (39.5%)	3 (50.0%)
Grade 2	8 (9.3%)	0
Grade 3	0	0
Grade 4	0	0
Grade 5	0	0
All Grade	42 (48.8%)	3 (50.0%)
(95% CI)	(37.9%, 59.9%)	(11.8%, 88.2%)
≥ grade 2	8 (9.3%)	0
(95% CI)	(4.1%, 17.5%)	(0.0%, 45.9%)
Occurrence of any CRS signs and symptoms[a]	**42 (100%)**	**3 (100%)**
Fever	42 (100%)	3 (100%)
Hypotension	6 (14.3%)	0
Hypoxia	2 (4.8%)	0
Other[b]	10 (23.8%)	1 (33.3%)
Subject requiring oxygen[a]	**2 (4.8%)**	**0**
Subject requiring vasopressor (excluding midodrine/midodrine hydrochloride, milrinone, vasopressin)[a]	**0**	**0**
Subject requiring vasopressin[a]	**0**	**0**
Subject with CRS[a]		
Treated with anti-cytokine therapy	10 (23.8%)	0
Tocilizumab	10 (23.8%)	0
Other anti-cytokine	0	0
Treated with corticosteroid for CRS	11 (26.2%)	1 (33.3%)
Leading to dose delay	16 (38.1%)	0
Leading to treatment discontinuation	0	0
Time to first CRS onset (days)[c]		
n	42	3
Mean (standard deviation)	19.6 (12.61)	9.7 (7.51)
Median	23.0	10.0
Min, max	1, 52	2, 17
Time to CRS resolution (days)		
Subjects with resolved CRS[a]	42 (100%)	3 (100%)
Mean (standard deviation)[d]	3.0 (2.64)	3.0 (1.73)
Median	2.0	2.0
Min, max	1, 14	2, 5

Abbreviations: AESI = adverse event of special interest; CI = confidence interval; CRS = cytokine release syndrome; FL = follicular lymphoma; max = maximum; min = minimum.
Arm A: Priming 0.16 mg, First Intermediate 0.8 mg, Second Intermediate 3 mg.
Arm B: Priming 0.16 mg, First Intermediate 0.8 mg, Second Intermediate 6 mg.
Note: CRS events are graded according to (Lee et al., 2019). The toxicity grade refers to the worst toxicity grade. For a subject with multiple events, a subject is defined as resolved if all events are resolved.
[a] Percentage calculated based on subjects with at least 1 CRS event.
[b] CRS signs and symptoms categorized as 'Other' are presented in Table 14.3.2.14.1.
[c] From first dose of epcoritamab to first CRS onset.
[d] Based on longest recorded CRS duration in subjects with >1 CRS event.
Data cutoff date: 08 Jan 2024
Source: Table 14.3.2.14.1

Table 55: Subject-Level Summary of CRS Events by Grouped Dosing Period – GCT3013-01 Optimization Part – FL 1-3A Cohort (Safety Analysis Set)

	Arm A		
	Dosing Period		
	Up to Second Full Dose[a,b] (N=86)	First Full Dose and After[c] (N=82)	Overall[d] (N=86)
Subjects with ≥1 CRS event	**42 (48.8%)**	**31 (37.8%)**	**42 (48.8%)**
Grade 1	34 (39.5%)	26 (31.7%)	34 (39.5%)
Grade 2	8 (9.3%)	5 (6.1%)	8 (9.3%)
Grade 3	0	0	0
Grade 4	0	0	0
Grade 5	0	0	0
All Grade	42 (48.8%)	31 (37.8%)	42 (48.8%)
(95% CI)	(37.9%, 59.9%)	(27.3%, 49.2%)	(37.9%, 59.9%)
≥ grade 2	8 (9.3%)	5 (6.1%)	8 (9.3%)
(95% CI)	(4.1%, 17.5%)	(2.0%, 13.7%)	(4.1%, 17.5%)
Subject requiring oxygen[e]	**2 (4.8%)**	**2 (6.5%)**	**2 (4.8%)**
Subject requiring vasopressor (excluding midodrine/midodrine hydrochloride, milrinone, vasopressin)[e]	**0**	**0**	**0**
Subject requiring vasopressin[e]	**0**	**0**	**0**
Occurrence of any CRS signs and symptoms[e]	**42 (100%)**	**31 (100%)**	**42 (100%)**
Fever	42 (100%)	31 (100%)	42 (100%)
Hypotension	6 (14.3%)	3 (9.7%)	6 (14.3%)
Hypoxia	2 (4.8%)	2 (6.5%)	2 (4.8%)
Other[f]	10 (23.8%)	9 (29.0%)	10 (23.8%)

	Arm A		
	Dosing Period		
	Up to Second Full Dose[a,b] (N=86)	First Full Dose and After[c] (N=82)	Overall[d] (N=86)
Subjects with CRS accompanied by[e]			
Tocilizumab	9 (21.4%)	6 (19.4%)	10 (23.8%)
Treated with corticosteroid for CRS	11 (26.2%)	7 (22.6%)	11 (26.2%)
Leading to dose delay	16 (38.1%)	13 (41.9%)	16 (38.1%)
Leading to treatment discontinuation	0	0	0
Time to CRS onset from most recent dosing (hours)			
n	42	31	42
Mean (standard deviation)[g]	56.0 (44.98)	66.2 (42.50)	56.0 (44.98)
Median	40.1	61.0	40.1
Min, max	6, 163	3, 178	6, 163
Time to CRS resolution (hours)[e]			
Subjects with resolved CRS[e]	42 (100%)	31 (100%)	42 (100%)
Mean (standard deviation)	60.2 (64.89)	59.5 (55.76)	60.8 (64.89)
Median[h]	48.0	48.0	48.0
Min, max	1, 322	1, 192	1, 322

Table 56: Event-Level Summary of AESI: Cytokine Release Syndrome – GCT3013-01 Optimization Part – FL 1-3A Cohort (Safety Analysis Set)

	Arm A (N=86)
Subjects with ≥1 CRS event	42
Number of episodes per subject[a]	
1 event	22 (52.4%)
2 events	15 (35.7%)
3 events	3 (7.1%)
4 events	2 (4.8%)
5 events	0
Number of CRS events	**69**
Grade 1	61 (88.4%)
Grade 2	8 (11.6%)
Grade 3	0
Grade 4	0
Grade 5	0
Occurrence of any CRS signs and symptoms	**69 (100%)**
Fever	69 (100%)
Hypotension	6 (8.7%)
Hypoxia	2 (2.9%)
Other[b]	12 (17.4%)
CRS events	
Treated with anti-cytokine therapy	10 (14.5%)
Tocilizumab	10 (14.5%)
Number of tocilizumab doses taken	
1	8 (11.6%)
2	2 (2.9%)
3	0
≥4	0
Other anti-cytokine	0
Treated with corticosteroid for CRS	13 (18.8%)
Leading to dose delay	17 (24.6%)
Leading to treatment discontinuation	0
Time from most recent dosing (days)	
n	69
Mean (std dev)	3.9 (2.09)
Median	4.0
Min, max	1, 8
Time to CRS resolution (days)	
Resolved CRS	69 (100%)
Mean (std dev)	2.6 (2.24)
Median	2.0
Min, max	1, 14

Table 57: Event-Level Summary of CRS Events by Dosing Period – GCT3013-01 Optimization Part – FL 1-3A Cohort (Safety Analysis Set)

	Arm A					
	Dosing Period					
	Priming (N=86)	Intermediate (N=85)	Second Intermediate (N=82)	First Full (N=82)	Second Full (N=81)	Third Full and After (N=75)
Subjects with ≥1 CRS event	**10**	**5**	**12**	**30**	**5**	**3**
Number of episodes per subject[a]						
1 event	10 (100%)	5 (100%)	12 (100%)	26 (86.7%)	5 (100%)	3 (100%)
2 events	0	0	0	4 (13.3%)	0	0
3 events	0	0	0	0	0	0
4 events	0	0	0	0	0	0
5 events	0	0	0	0	0	0
Number of CRS events	**10**	**5**	**12**	**34**	**5**	**3**
Grade 1	8 (80.0%)	5 (100%)	11 (91.7%)	29 (85.3%)	5 (100%)	3 (100%)
Grade 2	2 (20.0%)	0	1 (8.3%)	5 (14.7%)	0	0
Grade 3	0	0	0	0	0	0
Grade 4	0	0	0	0	0	0
Grade 5	0	0	0	0	0	0

Table 58: Summary of CRS Events by Dexamethasone, IV Fluids, and Dosing Period – FL Optimization Cohort vs FL Safety Pool 01

	GCT3013-01 FL Safety Pool 01 (ESC+EXP) Dosing Period[a]			GCT3013-01 FL Optimization Cohort (Arm A) Dosing Period[b]			
	Priming	Intermediate	First Full **Dose**	Priming	Intermediate	Second Intermediate	First Full **Dose**
	N=129	N=128	N=127	N=86	N=85	N=82	N=82
Premedication of dexamethasone/ IV Fluid							
Subjects with at least 1 dexamethasone	Dexamethasone: 30 (23.3%) Dexamethasone sodium phosphate: 1 (0.8%)			79 (91.9%)	79 (92.9%)	77 (93.9%)	79 (96.3%)
Subjects with at least 1 IV Fluid	No data[c]			70 (81.4%)	70 (82.4%)	72 (87.8%)	68 (82.9%)
Subjects with at least 1 dexamethasone and IV Fluid	No data[c]			67 (77.9%)	66 (77.6%)	68 (82.9%)	66 (80.5%)
CRS events by subject							
Subjects with at least 1 CRS event (any grade)	18 (14.0%)	16 (12.5%)	76 (59.8%)	10 (11.6%)	5 (5.9%)	12 (14.6%)	30 (36.6%)
Grade 1	12 (9.3%)	12 (9.4%)	49 (38.6%)	8 (9.3%)	5 (5.9%)	11 (13.4%)	25 (30.5%)
Grade 2	5 (3.9%)	4 (3.1%)	26 (20.5%)	2 (2.3%)	0	1 (1.2%)	5 (6.1%)
Grade 3	1 (0.8%)	0	1 (0.8%)	0	0	0	0
Grade 4	0	0	0	0	0	0	0
Grade 5	0	0	0	0	0	0	0

CRS = cytokine release syndrome; FL = follicular lymphoma; IV = intravenous.

a. Source: Data Update Table 2.8, Table 5.4; Table q26_1_1 (Data cutoff 16 Oct 2023)

b. Source: Study GCT3013-01-OPT-FL CSR Table 14.3.2.14.2, Table 14.3.2.14.12.1 (Data cutoff 08Jan2024); ISS Table 2.8, Table 5 (Data cutoff 21Apr 2023)

c. The recommendations for dexamethasone as the preferred corticosteroid (Optimization Part only) and the emphasis on adequate hydration in the GCT3013-01 study was officially introduced with protocol amendment 9 (Version 11.0, dated 07 July 2022). In previous protocol versions , there was no explicit recommendation for hydration during Cycle 1 in the Expansion part, and therefore data on IV fluid administration were not necessarily captured.

In the FL optimization cohort, 10 (14.5%) CRS events were treated with tocilizumab. All 10 of these events resolved after the administration of tocilizumab with a median time to resolution of 1.5 days (range: 1, 8). . Nine (90.0%) of these CRS events (5 grade 1 events and 4 grade 2 events) were treated with tocilizumab alone and 1 grade 2 CRS event treated with tocilizumab was also treated with additional corticosteroids (beyond the prophylactic doses required per protocol). The 59 CRS events (56 grade 1 events and 3 grade 2 events) not treated with tocilizumab resolved in a median of 2.0 days (range: 1, 14).

In contrast to the Expansion Part of Study GCT3013-01, hospitalization for the purpose of safety monitoring during or immediately following administration of the first full dose of epcoritamab was not required for subjects in the FL optimization cohort but was instead implemented per the investigator's discretion. Subjects who were not hospitalized were to remain in close proximity to the treatment facility (within 30 minutes distance) for 24 hours after the first full dose of epcoritamab (i.e., C1D22).

Of the 82 subjects in the FL optimization cohort who received the first full dose of epcoritamab, 38 (46.3%) had pre-planned hospitalization per the investigator's discretion: 18 (47.4%) had pre-planned hospitalization for monitoring potential CRS and 20 (52.6%) were hospitalized at the time for logistical/social/other medical reasons. The remaining 44 (53.7%) subjects were not hospitalized on the first full dose date. CRS events occurred in 13 of 38 (34.2%) subjects who were inpatients and in 17 of 44 (38.6%) subjects who were outpatients on the date of the first full dose.

Other adverse events

In Arm A, 27 (31.4%) subjects experienced **neurological events** (broad definition); 9 (10.5%) subjects experienced a neurological event considered related to epcoritamab by the investigator. The most common (≥5%) events were headache (12 subjects; 14.0%) and dizziness (7 subjects; 8.1%). One subject each experienced a grade 3 and grade 4 neurological event (broad definition). The grade 4 event was spinal cord compression related to progressive disease and was not considered related to epcoritamab by the investigator and that led to epcoritamab dose delay. The grade 3 event was headache that was considered related to epcoritamab by the investigator and that led to epcoritamab dose delay.

Thirty-five (40.7%) subjects in Arm A had at least 1 **cytopenia event** (broad definition). A total of 18 (20.9%) subjects experienced neutropenia (grouped) of which 9 (10.5%) subjects experienced grade 3 events, and 8 (9.3%) subjects experienced grade 4 events. Fifteen (83.3%) subjects with neutropenia required treatment with G-CSF. One (1.2%) subject experienced febrile neutropenia; the event was grade 3 and treatment with G-CSF was required. A total of 8 (9.3%) subjects experienced thrombocytopenia (broad) of which (1.2%) subject experienced a grade 3 event, and 1 (1.2%) subject experienced a grade 4 event. One (12.5%) subject with thrombocytopenia required treatment (platelet transfusion. A total of 11 (12.8%) subjects experienced anemia (broad) of which (2.3%) subjects experienced a grade 3 event. Four (36.4%) subjects with anemia required treatment, including packed red blood cell transfusions for 3 subjects, and ferrous glycine sulfate in 1 subject. A total of 11 (12.8%) subjects experienced lymphopenia (grouped) of which 7 (8.1%) subjects experienced grade 3 events, and 3 (3.5%) subjects experienced grade 4 events.

A total of 48 (55.8%) subjects in Arm A experienced at least 1 **infection event**. The most frequently reported TEAEs in the SOC Infections and infestations (≥5% of subjects) were COVID-19 (16 subjects; 18.6%) and oral candidiasis and rhinovirus infection (5 subjects each; 5.8%). TEAEs in the SOC Infections and infestations considered related to epcoritamab by the investigator were reported for 28 (32.6%) subjects, TEAEs reported in more than 1 subject include COVID-19 (6 subjects; 7.0%), pneumonia (3 subjects; 3.5%), and urinary tract infection, bronchitis, candida infection, conjunctivitis, and respiratory syncytial virus infection (2 subjects each; 2.3%).

Sixteen (18.6%) subjects in Arm A experienced at least 1 **serious infection** and 9 (10.5%) subjects experienced at least 1 serious infection considered related to epcoritamab by the investigator. The most common PTs were COVID-19 (4.7%), COVID-19 pneumonia (2.3%) and Urinary tract infection (2.3%). There were no fatal TEAEs in the optimization cohort and thus no Grade 5 infections.

Table 59 Summary of Serious Infections by SOC and PT – GCT3013-01 Optimization

System Organ Class Preferred Term	Arm A (N=86)		Arm B (N=6)	
	All	Related	All	Related
Infections and infestations	**16 (18.6%)**	**9 (10.5%)**	**1 (16.7%)**	**1 (16.7%)**
COVID-19	4 (4.7%)	2 (2.3%)	0	0
COVID-19 pneumonia	2 (2.3%)	1 (1.2%)	0	0
Urinary tract infection	2 (2.3%)	1 (1.2%)	0	0
Escherichia infection	1 (1.2%)	1 (1.2%)	0	0
Herpes zoster	1 (1.2%)	1 (1.2%)	0	0
Infection	1 (1.2%)	1 (1.2%)	0	0
Pneumocystis jirovecii pneumonia	0	0	1 (16.7%)	1 (16.7%)
Pneumonia	1 (1.2%)	0	0	0
Pneumonia viral	1 (1.2%)	1 (1.2%)	0	0
Pseudomonal bacteraemia	1 (1.2%)	1 (1.2%)	0	0
Rhinovirus infection	1 (1.2%)	0	0	0
Skin bacterial infection	1 (1.2%)	0	0	0
Vascular device infection	1 (1.2%)	1 (1.2%)	0	0

Abbreviations: COVID-19 = coronavirus disease 2019; FL = follicular lymphoma; PT = preferred term; SOC = system organ class.
Arm A: Priming 0.16 mg, First Intermediate 0.8 mg, Second Intermediate 3 mg.
Arm B: Priming 0.16 mg, First Intermediate 0.8 mg, Second Intermediate 6 mg.
Note: Percentages calculated based on number of subjects in Safety Analysis Set. Adverse events are classified using Medical Dictionary for Regulatory Activities v26.1 and are counted only once per SOC and only once per PT.
Data cutoff date: 08 Jan 2024
Source: Table 14.3.2.13.1

COVID-19; The FL Optimization Part of the GCT3013-01 trial was conducted after the surge from Omicron and subsequent variants. The first subject signed informed consent on 17 Oct 2022 and the clinical data cutoff date was 08 Jan 2024.

Table 60: Overview of COVID-19 Relevant Adverse Events – GCT3013-01 Optimization Part – FL 1-3A Cohort (Safety Analysis Set)

Number of Subjects with ≥1 Relevant COVID-19 TEAE, n (%)	Arm A (N=86)		Arm B (N=6)	
	All	Related	All	Related
Any TEAE	**85 (98.8%)**	**78 (90.7%)**	**6 (100%)**	**5 (83.3%)**
COVID-19	16 (18.6%)	6 (7.0%)	**2 (33.3%)**	0
COVID-19 pneumonia	2 (2.3%)	1 (1.2%)	0	0
Any Grade 3 or 4 TEAE	**46 (53.5%)**	**29 (33.7%)**	**3 (50.0%)**	**2 (33.3%)**
COVID-19	4 (4.7%)	1 (1.2%)	0	0
COVID-19 pneumonia	1 (1.2%)	0	0	0
Any Serious TEAE	**38 (44.2%)**	**31 (36.0%)**	**4 (66.7%)**	**3 (50.0%)**
COVID-19	4 (4.7%)	2 (2.3%)	0	0
COVID-19 pneumonia	2 (2.3%)	1 (1.2%)	0	0
Any Fatal TEAE	**0**	**0**	**0**	**0**
COVID-19	0	0	0	0
COVID-19 pneumonia	0	0	0	0
Any TEAE leading to treatment discontinuation	**3 (3.5%)**	**3 (3.5%)**	**0**	**0**
COVID-19	0	0	0	0
COVID-19 pneumonia	0	0	0	0
Any TEAE leading to dose delay	**50 (58.1%)**	**31 (36.0%)**	**4 (66.7%)**	**1 (16.7%)**
COVID-19	15 (17.4%)	6 (7.0%)	1 (16.7%)	0
COVID-19 pneumonia	1 (1.2%)	1 (1.2%)	0	0

Abbreviations: COVID-19 = coronavirus disease 2019; FL = follicular lymphoma; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.
Arm A: Priming 0.16 mg, First Intermediate 0.8 mg, Second Intermediate 3 mg
Arm B: Priming 0.16 mg, First Intermediate 0.8 mg, Second Intermediate 6 mg
Note: Adverse events are classified using MedDRA v26.1 and are counted only once per category.
Data cutoff date: 08 Feb 2024
Source: Table 14.3.1.2.1, Table 14.3.1.11.1, Table 14.3.2.13.1, Table 14.3.2.12.1, Table 14.3.1.9.1, Table 14.3.1.10.1, and Listing 16.2.7.4.

Injection site reaction events were experienced by 28 (32.6%) subjects in Arm A. All events were grade 1 or 2 and most subjects experienced a single episode of injection site reaction.

In Arm A, 1 (1.2%) subject had a **tumor flare event**. This subject had an event of grade 2 tumor flare with a time to first onset of 34.0 days. The event resolved in 9.0 days with no treatment required.

In Arm A, **hematological laboratory** grade 4 worst post-baseline results were observed for absolute lymphocytes count (decrease) in 24 (28.2%) subjects, absolute neutrophils count (decrease) in 11 (12.8%) subjects, and platelets (decrease) in 2 (2.3%) subjects. Grade 3 worst post-baseline results were observed for absolute lymphocytes count (decrease) in 43 (50.6%) subjects, absolute neutrophils count (decrease) in 13 (15.1%) subjects, and hemoglobin (decrease) in 5 (5.8%) subjects.

Grade 3 **biochemistry laboratory** worst post-baseline results were observed for potassium (decrease) in 4 (4.7%) subjects, and for total bilirubin (increase), alanine aminotransferase (increase), and aspartate transaminase (increase) in 1 (1.2%) subject each. No subject met potential Hy's Law criteria.

At baseline, 5 (5.8%) subjects had **QTcF interval** >450 to 480 ms, and 1 (1.2%) subject had QTcF interval >480 ms. During the treatment period, QTcF interval >450 to 480 ms was observed in 15 (18.1%) subjects, QTcF interval >480 to 500 ms was observed in 2 (2.4%) subjects, and QTcF interval >500 ms was observed in 3 (3.6%) subjects with FL. Episodes of QTcF >500 ms were infrequent and occurred in 3 subjects in Arm A. One of the 3 subjects had an episode that was considered clinically significant. No study drug actions were taken. All three subjects had at least 1 of the following risk-

factors: 1) relevant prior or ongoing cardiac disease/conditions or 2) relevant concomitant medications which could affect QTc interval. None of the events were considered by the sponsor to be directly related to the administration of epcoritamab.

Post marketing experience

N/A.

2.5.1. Discussion on clinical safety

Analysis sets – The primary safety population (Safety Pool 01 R/R FL [N=129]) included all R/R FL subjects who were assigned to the 48 mg full dose and received at least 1 dose of epcoritamab in the Escalation or Expansion Parts of Study GCT3013-01. Safety data from the primary safety population are reported below unless it is stated otherwise. Part of the data from the primary safety analysis set has been previously reported as supportive data in the initial MAA for the DLBCL indication. Supportive safety data came from two safety pools (which also included the Safety Pool 01 R/R FL); Safety Pool 01+04 R/R FL; N=151 and Safety Pool (01+04) All B-NHL (N=449). A data cutoff date of 21 April 2023 was used for these safety pools. In addition, safety data have been provided from FL patients (N=30) in the iNHL cohort an ongoing Optimization Part in Study GCT3013-01 using a clinical data cut-off date of 31 Jul 2023. The FL cohort investigates an alternative 3 step SUD regimens along with additional measures to reduce CRS; hydration recommendations, dexamethasone (15 mg) premedication in Cycle 1, re-priming instructions and dose modifications for CRS events. The regimen is investigated to reduce the risk of ≥ Grade 2 CRS and all grade CRS.

Exposure – In the primary safety population the median duration of treatment was 8.3 months and 37.2% of subjects received at least 12 months of treatment. The extent of exposure is considered acceptable considering the disease setting. Long-term safety remains missing information in the safety concerns. The MAH should provide a final CSR of the iNHL cohort of the GCT3013-01 study as a SOB. Overall, 68.2% of subjects required a dose delay, including 58.9% of subjects due to an AE and 27.1% of subjects who required a dose delay for another reason, including COVID-19 control measures. The median exposure was longer in the primary safety population compared to the All B-NHL safety pool (6.2 months, probably due to differences in prognosis).

AEs – Overall almost all patients experienced any Grade TEAEs (98.4%) and most patients had a severe TEAE (69.0%). TEAEs reported in ≥ 15% of subjects included CRS (66.7%), injection site reaction (36.4%), COVID-19 (31.0%), fatigue (30.2%), diarrhea (26.4%), pyrexia (not attributed to CRS; 24.8%), neutropenia (20.2%), headache (19.4%), injection site erythema (17.8%), nausea (17.1%), cough (17.1%), constipation (15.5%). No new safety signals are reported, however TEAEs in SOCs infections and infestations (77.5% versus 64.4%), skin and subcutaneous tissues disorders (48.8% versus 37.6%), respiratory, thoracic and mediastinal disorders (43.4% versus 34.1%) were observed more frequently in Safety Pool 01 R/R FL patients compared to the All B-NHL safety pool. Due to the lack of a comparator the reason for these differences remains unknown (disease or (previous) treatment-related).

Severe TEAEs reported in ≥ 5% of subjects included neutropenia (17.1%), COVID-19 (10.9%), neutrophil count decreased (9.3%) and anaemia and lymphopenia (both 6.2%). The most frequently reported (in ≥ 10% of subjects) treatment-related TEAEs included CRS (66.7%), injection site reaction (36.4%), fatigue (18.6%), neutropenia (18.6%), injection site erythema (17.1%), pyrexia (12.4%), and diarrhea (10.9%). The most frequently reported Grade 3 or 4 drug-related TEAEs (in ≥ 5% of the patients) were neutropenia (15.5%) and neutrophil count decreased (7.0%). Treatment-related TEAEs

were mostly comparable across the safety pools.
As in the initial MAA the safety database is based on single arm studies with no comparator and causality assessment of certain adverse events is challenging due to overlapping symptoms of the underlying diagnosis and toxicity from previous anticancer therapies.

SAEs - Serious TEAEs were reported for 69.0% of subjects. The most frequently reported (in ≥ 5% of subjects) serious TEAEs included CRS (41.9%), COVID-19 (11.6%), COVID-19 pneumonia (7.8%), and pneumonia (5.4%). CRS as SAE was observed in a slightly lower frequency in the two other safety pools, (39.1% and 35.9%), while the frequency of the other SAEs were more or less comparable across the safety pools.

Deaths – In total 13 fatal TEAEs (10.1%) were reported. There were 5 deaths (3.9%) due to COVID-19 pneumonia and 1 due to COVID-19, thus in total 4,7% due to COVID-19. The other fatal TEAEs were due to infections (pneumonia, pseudomonal sepsis organising pneumonia; one each), interstitial lung disease, cardiopulmonary failure, lymphoma transformation and MDS (one each), the latter was diagnosed 7 days after enrolment. None of the fatal TEAE in the Safety Pool 01 R/R FL were considered related to the study drug by the investigator. However, especially for the fatal TEAEs in the SOC Infections and infestations a contributory role of epcoritamab cannot be ruled out completely (see below). In the Safety Pool 01+04 All B-NHL fatal TEAEs were observed in 10.5% of the patients. Six (1.3%) subjects experienced drug-related fatal TEAEs, including 2 (0.4%) subjects each with CRS and ICANS and 1 (0.2%) subject each with COVID-19 pneumonia and pneumonia bacterial. Of note, in the Safety Pool 01+04 All B-NHL (41.4%) deaths were more common compared to the primary population (26.4%). This appears to be related to the worse prognosis in these patients as the differences are mainly due to deaths due to disease progression (respectively 26.1% versus 9.3%).

AESIs – CRS is an important identified risk and is frequently observed in the primary safety population (66.7%). Most CRS events are low-grade and there were 2 Grade 3 events (1.6%). Most patients had 1 CRS event, but multiple CRS episodes were also observed (2 episodes (19.8%)- 6 episodes (1.2%)). Most CRS events were observed after the first full dose (59.8%), followed by the priming (14.0%) and intermediate dose (12.5%). CRS led to dose delay/interruption in 17.4% of the patients, but did not lead to discontinuations. All CRS cases resolved in a median time to resolution of 2.0 days (range 1,54). In the All B-NHL safety pool the number of CRS events was comparable (64.4%). Grade 3 events were seen in 4.7%. There were two MCL patients (0.4%) with Grade 4 CRS and two patients (1 MCL, 1 with iNHL) with Grade 5 CRS (0.4%). In the All B-NHL safety pool CRS led to discontinuation in 4 (1.4%) patients. In this pool CRS was not resolved in 5 patients (in the two patients with Grade 5 events, and in 3 patients that died due to disease progression). Starting from amendment 9 in the GCT3013-01 study additional measures for sufficient fluid intake were recommended as well as other measures to reduce CRS. However, all but one patient were already included in the study and beyond Cycle 1 at the time of this amendment. The additional CRS management measures did apply to all the optimization cohort and are discussed in more detail below.

ICANS is also an important identified risk and was seen in 6.2% of the patients in the primary safety population. No severe cases were observed. ICANS led to dose delay in 1 (12.5%) subject. No ICANS led to treatment discontinuation. All ICANS events had resolved by the data cutoff date, with the median time to ICANS resolution being 2.0 days. In 6 subjects, the ICANS overlapped with CRS events. In Safety Pool with All B-NHL the frequency of patients with ICANS was comparable to the primary safety population. In this pool one (0.2%) subject experienced Grade 4 ICANS and 2 (0.4%) subjects experienced Grade 5 ICANS.

TLS was not observed in the primary safety population. In the All B-NHL safety pool there were 7 patients with TLS, of which 4 (0.9%) were Grade 3 TLS.

Other safety topics – Serious infections are an important identified risk for epcoritamab. In total, 40.3% subjects experienced at least 1 serious infection, with the most frequently reported PTs (in ≥ 5% of subjects) being COVID-19 (11.6%), COVID-19 pneumonia (7.8%), and pneumonia (5.4%). This is consistent with the known safety profile. Serious events in the SOC of Infections and Infestations were considered related to epcoritamab by the investigator in 12 (9.3%) subjects. Fatal events were reported in 8 (6.2%) subjects (6 deaths were due to COVID -19 and one each due to pneumonia and pseudomonal sepsis organising pneumonia). None of the fatal serious infections were considered related to epcoritamab by the investigator. Serious infections leading to treatment discontinuation were reported in 14 (10.9%) subjects and events leading to dose delay were reported in 32 (24.8%) subjects. In the primary safety population serious infections were observed at a slightly higher frequency compared to the All B-NHL safety pool (40.3% versus 34.7%), the reason for this is unknown. Updated data on serious infections with a DCO of 16Oct2023 has not led to any significant changes in the frequency or severity of these events. As of the DCO of 16 October 2023 the number of serious infections was 42.6%; the most frequently reported PTs (in ≥ 2% of subjects) were COVID-19 (14.0%), COVID-19 pneumonia (9.3%), pneumonia (6.2%), and Pneumocystis jirovecii pneumonia (2.3%). Grade 5 events of infection occurred in 9 (7%) patients, 6 (4.7%) of which were attributed to COVID-19 or COVID-19 pneumonia.

The number of serious infections appears to be higher compared to another recently approved drug for FL (EPAR Lunsumio serious infections 17.0%; fatal infections 0.9%). Whether this is due to epcoritamab, due to COVID-19 alone, due to the disease, due to prior treatments, and/or due to the limitations of cross-study comparisons is uncertain. The uncontrolled study designs hinders certain conclusions on this issue. In general, bispecific antibodies are known to be associated with an increased infection risk. Literature indicates that patients with B-cell malignancies, particularly RR FL patients, age ≥ 70 years have a higher risk for COVID-19 mortality compared to other lymphoma patients. Also recent administration of anti-CD20 therapy may be a risk factor. For NHL patients an overall mortality rate for hospitalized COVID-19 patients ranging from 19%-35% has been reported. However, these data are based on retrospective studies with moderate sample sizes. In addition, the MAH has provided literature studies (Villaboas 2023, Galusic 2022, Paszkiewicz-Kozik 2023, Nachar 2023) concerning FL/NHL patients in the same period as the pivotal study. These studies indicate different frequencies of COVID-19 infections, although this may be influenced by many factors including method of collection and study population. Reassuring is that a comparable number of COVID-19 infections is observed compared to the only phase 2 study (Villaboas 2023), which has also been conducted in R/R FL patients. It is also reassuring that the number of deaths due to COVID-19 and the number of fatal infections in the pivotal study is comparable or lower compared to the other studies. Of note, in the optimization cohort, for which the study was conducted after the COVID-19 pandemic, the number of serious infections was 18.6%. The most common PTs were COVID-19 (4.7%), COVID-19 pneumonia (2.3%) and Urinary tract infection (2.3%). There were no fatal TEAEs in the optimization cohort and thus no Grade 5 infections were reported. The frequencies of serious and fatal infections observed in the optimization cohort are much lower compared to the expansion cohort. They are also in line with data from similar products for which studies were conducted prior to the COVID-19 pandemic. Therefore, these data provide some reassurance that the observed infection rates may not be treatment-related but rather related to the COVID-19 pandemic.

Overall, the provided data provide reassurance that the (COVID-19) infection and death rates observed in the pivotal study are not outliers, however considering the uncontrolled nature of the pivotal study full reassurance cannot be provided. This issue should be assessed in the confirmatory study. No risk factors relevant for risk minimalization could be identified in patients with serious infections.

Neurological events were observed in comparable rates in the primary safety population compared to the ALL B-NHL safety pool using a broad definition 48.1% versus 41.0%) and Topp definition

(31.8% versus 29.8%). Using both definitions three (2.3%) severe neurological events were seen; Bell's palsy, dizziness, and syncope (1 subject each; all Grade 3). Around 40% of the patients with neurological events were not resolved at the database lock. In the All NHL safety pool one (0.2%) patient with MCL experienced Grade 4 and 2 (0.4%) patients (1 with DLBCL and 1 with MCL) reported Grade 5 neurological events (all ICANS).

Cytopenia events were frequently observed (46.5%) with 37.2% ≥ Grade 3 events and multiple episodes per patient were observed. Febrile neutropenia was seen in 4 patients (3.1%). For neutropenia and febrile neutropenia the majority of patients received G-CSF treatments (in the case of recurring Grade ≥3 neutropenia, use of growth factors was mandated). As G-CSF could be considered standard practice in lymphoma patients, it is not needed to report this in the label.

Injection site reactions were observed in 56.6% of the subjects, all of which were drug-related. The most frequently reported (≥ 5% of subjects) events included injection site reaction (36.4%), injection site erythema (17.8%), and injection site rash (7.8%). Three (2.3%) subjects experienced injection site reactions leading to dose delay. No subject experienced injection site reactions leading to treatment discontinuation.

Data on neurological events, cytopenia events and injection site reactions from the two other safety pools were largely comparable to the primary safety population.

COVID-19 - Additional exploratory analyses were performed to assess the impact of COVID-19 on patients with FL in the expansion part of Study GCT3013 01 (Study GCT3013-01-EXP-iNHL; N=128). In total 14 (10.9%) subjects with FL had a death associated with COVID-19. The median age of the 14 subjects with FL who died was 73.0 years, with 4 (28.6%) subjects ≥75 years of age.

Overdose – The risk of overdose due to medication errors is an important potential risk for epcoritamab. As of the 21 April 2023 data cutoff date, 1 medication error has been reported in FL subjects receiving epcoritamab monotherapy in the primary safety population. This medication error was an overdose (> 10% protocol-prescribed dose) in the priming dose during the Escalation Part of Study GCT3013-01; the intended epcoritamab dose was 0.08 mg, but the subject was administered a dose of 0.96 mg. There were no adverse events reported due to this overdose. In Dose Escalation, 3 subjects received a full planned dose of 60 mg with no unexpected adverse effects. The MAH indicates that there were no medication errors in R/R FL subjects from the GCT3013-04 study.

Laboratory findings – Grade 3-4 haematology laboratory abnormalities (in ≥10% of the patients) that frequently occurred were low lymphocytes count (81.6%), low neutrophil count (29.9%), low white blood cell count (18.6%) and low hemoglobin (10.2%). The hematologic laboratory findings are expected for the MoA and disease to be treated. Grade 3-4 biochemistry abnormalities (in ≥5% of the patients) were elevated ALAT (7.8%) and ASAT (5.4%). In the primary safety population 3 (2.3%) subjects had AST or ALT > 3 × ULN and total bilirubin > 2 × ULN within 30 days of epcoritamab administration. It is agreed with the MAH that a DILI is unlikely in these 3 subjects as they had alternative aetiologies for the abnormal hepatic laboratory results, including concurrent CRS (2 subjects) and hepatitis E (1 subject).

Immunogenicity – No pooled ADA analysis was possible due to the use of different assays in the GCT3013-01 and -04 studies. In the Study GCT3013-01 (ESC+EXP) R/R FL cohort, of the 120 immunogenicity-evaluable subjects treated with the 48-mg full dose of epcoritamab, on-treatment ADA status was positive for 3 (2.5%) subjects; all subjects were transiently ADA positive at one time point (1 C1D22/C2D1/C3D1) and ADA negative for all other time points. In the Study GCT3013-04 (ESC+EXP) R/R FL cohort 1 patient (out of 21 immunogenicity-evaluable subjects treated with the 48-mg full dose) was transiently ADA-positive from C1D22 through C2D1, then was ADA-negative for all subsequent time points. Of 71 immunogenicity-evaluable subjects in Arm A of the FL optimization

cohort of study GCT3013-01, on-treatment ADA status was positive for 5 (7.0%) subjects. None of the positive evaluations had titer ≥1. Neutralizing antibodies were not tested for as the Nab assay was only qualified for serum samples. The absence of Nab results makes the interpretation of the significance of the observed ADA levels challenging. However, the incidence of ADAs in both the expansion and optimization cohorts of study GCT3013-01 is relatively modest and therefore not considered a major concern. A meaningful analysis of the impact of ADAs on safety is also not possible due to the small sample.

Vital signs – Data on vital signs was only given per study. There were 6 (7.1% of the N = 128) subjects with FL the GCT3013-01 study Expansion Part iNHL cohort where a QTcF interval >500 msec was observed and also in 2 subjects with other subtypes. One event was reported as a Grade 3 AE of ECG QT prolonged, which was considered to be unrelated to epcoritamab; this subject had concurrent Grade 2 hypocalcaemia and Grade 2 hypokalaemia. In the primary safety population laboratory abnormalities in calcium and potassium observed in less than <25% of the patients and severe abnormalities are infrequent. Data from the GCT3013-01 study Expansion Part aNHL and MCL cohort reported comparable frequencies for QTcF interval >500 msec. Considering the low frequency of cardial AEs it can be supported that in the initial MAA it was concluded that there are no signals that epcoritamab has a clinically relevant effect on cardiac repolarization.

Special populations - Several safety subgroup analyses were conducted. Most noteworthy were analyses per age where higher frequencies of ≥ Grade 3 AEs, SAEs, AEs leading to discontinuation, were observed with increasing age (<65, 65-75, ≥75). This trend was also observed with serious CRS, serious infections, cytopenia and febrile neutropenia. Further, ≥ Grade 3 drug-related AEs and drug-related serious AEs and AEs leading to dose delay were observed in lower frequencies in female patients, while fatal AEs and AEs leading to discontinuation were observed in higher frequencies in female patients compared to males. Higher frequencies of severe AEs, SAEs and tolerability are observed in the subgroup of patients not double refractory to anti-CD20 and alkylating agent compared to the double refractory subgroup. Differences in safety per age and gender subgroup were not noted in DLBCL patients. Differences in safety in subgroups per age, gender and refractoriness to previous therapy may be due to differences in patient and disease characteristics, or differences in exposure. However, since in almost all AE categories relevant for elderly patients the subgroups of older patients (age 75-84 and age 65-74) report higher frequencies of AEs compared to younger patients (age <65), it is considered that it should be reported in section 4.8 under special populations that older patients may experience more severe toxicity compared to younger patients. This statement will need to be re-evaluated once the MAH has submitted the confirmatory study. At that time it can also be assessed whether this is related to epcoritamab only or also seen in the control arm.

Renal impairment - In general, the frequency and severity of events by renal function were comparable between patients with normal, mildly impaired and moderately impaired renal function at baseline, except for fatal TEAEs and TEAEs leading to discontinuation. Due to the small patient numbers and the lack of a control arm, it is unclear what is the cause of these numbers, however since exposure is comparable between patients with normal renal function and renal impairment, this issue is not further pursued.

Hepatic impairment – Higher frequencies of serious TEAEs, severe TEAEs, serious infections, CRS and cytopenia were observed in patients with mild hepatic dysfunction compared to patients with normal hepatic function at baseline. In the All B-NHL safety pool differences in Grade 3 or 4 TEAE (69.8% versus 79.7%) and in serious TEAE (64.2% versus 78.4%) were observed and other differences were not so outspoken as in the Safety Pool 01 R/R FL. Due to the small sample (N=21 patients with hepatic dysfunction) it cannot be concluded (nor excluded) whether patients with hepatic

impairment have worse toxicity compared to those with normal hepatic function. As there are no differences in exposure in patients with and with hepatic impairment, this issue is not further pursued.

Discontinuations, dose delays due to TEAEs - Discontinuations due to TEAEs were frequent (18.6%). TEAEs leading to treatment discontinuation reported in more than 2% of subjects (2 subjects) included COVID-19 pneumonia (5.4%) and COVID-19 (3.9%). The supportive safety analysis pool showed a similar profile. In Safety Pool 01 R/R FL (N=129), 59.7% of subjects experienced at least 1 TEAE leading to dose delay; in 34.9% of subjects, events were considered drug-related. The most frequently reported (in ≥ 5% of subjects) TEAEs leading to dose delay included COVID-19 (21.7%, 4.7% assessed as drug-related) and CRS (11.6%, all drug-related). Other frequently reported TEAEs were pneumonia (4.7%), upper respiratory tract infection (4.7%) and neutropenia (4.7%). The two supportive safety pools showed similar data.

Optimization part step up dosing for FL- During the initial MAA a REC for providing the step-up dosing (SUD) optimization cohort of Study GCT3013-01 in DLBCL, MCL and FL patients was raised. – Analysis of FL Optimization Cohort" (N= 86) has been provided (planned sample N=80). A new posology (3 step SUD schedule) for FL patients is proposed based on these data. In this schedule 3 mg is given as a second intermediate dose on D15, instead of the first full dose (48 mg) in the current posology. In addition, adequate hydration measures and dexamethasone (15 mg) premedication (instead of prednisone or dexamethasone in the current posology) was recommended in Cycle 1. Detailed repriming instructions and additional guidance on treatment modifications due to CRS events were also recommended. A study arm with a 6mg intermediate dose was discontinued.

As of the data cutoff date of 08 January 2024, the median duration of trial follow-up in the GCT3013-01 FL optimization cohort (N=86) was 5.7 months with a median treatment duration of 3.8 months). Baseline characteristics of the FL optimization cohort are largely comparable with the pivotal study cohort. In general a comparable safety profile is observed in the optimization cohort compared to the pivotal study cohort and no new safety concerns are raised. The median duration of treatment and follow up are shorter in the optimization cohort versus the pivotal study cohort. This likely influenced that some AEs are observed at a lower frequency in the optimization cohort compared to the pivotal study cohort, such as severe AEs, serious AEs and AEs leading to discontinuation. Less CRS events are observed in the optimization cohort (48.8%) versus the pivotal study cohort (66.7%). This is mainly due to a difference in Grade 2 events (9.3% vs. 24.8%) and Grade 3 events (0% vs. 1.6%). As most CRS events occur in Cycle 1, it is considered that the shorter follow up time of the optimization cohort compared to the expansion cohort is of minimal influence on these results. In conclusion, the safety profile seems comparable between the expansion cohort and the optimization cohort, while a clinically relevant reduction in the number of (Grade 2) CRS events is observed for the optimization cohort compared to the expansion cohort. The addition of the 3-step SUD regimen, as well as CRS management recommendations (see below) to section 4.2 of the SmPC is therefore considered acceptable. Since the treatment duration and follow-up in the optimization cohort is still limited, the MAH will provide the final safety data for the FL optimization cohort as part of SOB.

All patients in the optimization part received CRS management in accordance with amendment 9, as well as the new 3-SUD regimen. However, it is difficult to determine whether the reduction in CRS is due to the changes in posology or due to the changes in CRS management. Therefore, it is agreed with the MAH that section 4.2 of the SmPC should outline the same measures for CRS management that were implemented in PA9. Section 4.2 is largely in accordance with protocol amendment 9. The MAH has proposed a footnote to further clarify that dexamethasone is a preferred corticosteroid. This is considered acceptable. However, several differences are noted with the recommendations protocol amendment 9 and the proposed SmPC section 4.2. Further amendments were made to section 4.2 of the SmPC to fully align CRS management with the protocol.

The MAH also proposes that hospitalization is not needed for FL patients 24 hours after administration of the Cycle 1 Day 15 dose of 48 mg. For the primary safety population hospitalization for the first full dose was mandatory. Hospitalization for the administration of the first full dose of epcoritamab was not mandated in the FL dose optimization cohort. In the optimization cohort, about half of the study objects were hospitalized when given the first full dose. A similar incidence of CRS events was observed in inpatients (34.2%) and outpatients (38.6%). The severity of CRS events was similar in inpatients and outpatients; 5.3% inpatients and 6.8% of outpatients experiencing Grade 2 CRS events. All CRS events were managed appropriately and resolved. Acknowledging that the patient groups (inpatients and outpatients) may be not be homogenous due to patient selection, the median time to onset seemed to be similar. However, considering the wide range in time to onset, it is uncertain whether the requirement of 24-hours hospitalization after the first full dose would have any significant impact on the handling or outcome of CRS events. Training and education of patients in proper CRS identification and management, including the use of patient alert card, together with proximity to the treatment facility might be of similar importance. It is agreed that mandatory hospitalization for the first full dose is not required for FL patients.

Change in the expression of the pharmaceutical form to mitigate risk of medication errors

The 4 mg vial is used both as a concentrate for preparation of the 0.16 mg and 0.8 mg dose and undiluted for the 3 mg dose used in the 3 step-up schedule for the new indication. This implies that the pharmaceutical form should be changed from "concentrate for solution for injection" to "solution for injection". This is in line with policy for standard terms of the EDQM. As long as the medicinal product is intended to be used without dilution for at least one indication or part of a regime of treatment, then it can be referred to simply as 'Solution for injection'. However, the CHMP was concerned that change in the pharmaceutical form and strength may increase the potential risk of medication errors due to the different dilution steps as 4 mg/0.8mL vial was proposed both for direct injection and as a concentrate with dilution prior to injection. At initial MA, risk of overdose was listed in the RMP due to the complex dose preparation which included dilution in one or two steps. The MAH acknowledged the concerns and as additional mitigation measures to minimize the medication errors agreed to update the labelling on the outer carton with a statement to clearly outline in a red bolded colour which dose is diluted and which one is not: "Dilute prior to SC use for 0.16 mg and 0.8 mg doses. No dilution required for 3 mg dose". The MAH has also agreed to change pharmaceutical form from "concentrate for solution for injection" to "solution for injection", which is in line with policy for standard terms of the EDQM. The SmPC and Annex A have been updated accordingly.

Conditional Marketing authorisation

The product currently has a conditional marketing authorisation and it is considered that also for the R/R FL population, data are deemed non comprehensive and confirmatory data should be provided as the safety database is based on non-comparative data and limited in size and follow-up. Consequently, the MAH has provided a comparison of safety data with other therapies approved for FL with the following therapies with full approval: R2, BR, GB, ibritumomab tiuxetan, idealisib, duvelisib, zanubrutinib axicabtagene ciloleucel and tisagenlecleucel. The number of ≥Grade 3 AEs for epcoritamab is lower compared to duvelisib, axi-cel and tisa-cel, but comparable or higher compared to R2, GB and idealisib. As ibritumomab has been withdrawn in the EU, no further discussion is necessary. Epcoritamab does not appear to have lower numbers of SAEs compared to R2, GB, duvelisib, axi-cel, tisa-cel. The number of AEs could not be compared to BR and ibritumomab. In terms of discontinuation, only a lower number of discontinuations compared to duvelisib is observed, but not compared to other therapies (or the number of discontinuation is not known for these therapies). In terms of Liso-cel a differential safety profile in line with other CAR-T therapies (axi-cel, tisa-cel) is observed.

Compared to mosunetuzumab which has a CMA for FL, several safety aspects of epcoritamab appear comparable, except that for mosunetuzumab less discontinuations are reported as well as les SAEs. Thus, it is also not evident whether epcoritamab has a comparable safety profile compared to mosunetuzumab.

An analysis of epcoritamab compared to mosunetuzumab and axi-cel in institutional resources was also provided. The methods for the institutional resource analysis are very unclear and time required from clinical personnel and chair time were based on estimations rather than measurements. Therefore, the outcomes of this comparison are considered very unreliable and thus, they are not further discussed here.

Additional safety data needed in the context of a conditional MA

Additional confirmation of safety and efficacy of epcoritamab in the treatment of R/R FL after two or more lines of systemic therapy is needed. The MAH will submit results from study M20-638, a phase 3, open-label study of epcoritamab in combination with R2 compared to R2 in subjects with RR FL, which is acceptable. In addition, the MAH will submit the final results from the iNHL expansion cohort and the FL optimisation cohort from study GCT3013-01.

2.5.2. Conclusions on clinical safety

The safety profile for epcoritamab in R/R FL patients is in line with the known safety profile for epcoritamab. The safety profile is also in line with what can be expected for a bispecific CD3/CD20-directed T-cell engager. Due to the MoA of activating T-cells CRS, ICANS, and CTLS are to be expected, as are cytopaenias and infections with bispecific antibodies. 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. Literature studies provide reassurance that the (COVID-19) infection and death rates observed in the pivotal study are not outliers, however considering the uncontrolled nature of the pivotal study full reassurance cannot be provided pending the data from the confirmatory study. Limitations of the safety database are that it is based on non-comparative data and on a limited sample size and follow-up time. Therefore, additional data are considered needed in the context of a CMA.

A new posology introducing an additional intermediate dose is introduced. A comparable safety profile is observed in the optimization cohort compared to the pivotal study cohort and no new safety concerns are raised, while a clinically relevant reduction in the number of (Grade 2) CRS events is observed for the optimization cohort compared to the expansion cohort. The addition of the 3-step SUD regimen, as well as CRS management recommendations to section 4.2 of the SmPC is therefore considered acceptable.

The following measures are considered necessary to address issues related to clinical safety:

- In order to confirm the safety and efficacy of epcoritamab in the treatment of R/R FL after two or more lines of systemic therapy, the final CSRs including efficacy and safety analyses, for the iNHL expansion cohort and FL optimization cohort of study GCT3013-01 should be submitted (RMP Category 2).
- In order to confirm the safety and efficacy of epcoritamab in R/R FL, the MAH will submit the final CSR from study M20-638, a phase 3, open-label study of epcoritamab in combination with R2 compared to R2 in subjects with RR FL (RMP Category 2).

2.5.3. PSUR cycle

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.

2.6. Risk management plan

The MAH submitted an updated RMP version 1.4 with this application.

As a response to the 2nd RSI, the MAH submitted an updated RMP version (version 2.2, June 2024). RMP version 2.2 is acceptable.

Safety concerns

Table 61 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

Pharmacovigilance plan

Summary of planned additional PhV activities from RMP

Table 62: 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~~**4 of**~~2026~~ **2030**

Study/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
GCT3013-05: Randomized, OL, Ph3 Trial of Epcoritamab vs IC Chemotherapy in R/R DLBCL Ongoing	Evaluate safety and efficacy of epcoritamab compared to SOC (RGemOx 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				
M20-638: A Ph3, OL Trial of Epcoritamab in Combination with R^2 compared to R^2 in R/R FL **Ongoing**	**Evaluate the safety and efficacy of epcoritamab in combination with R^2 compared to R^2 alone**	**Long-term safety (maximum 5 years after last patient's first dose, treated until disease progression unless meet treatment discontinuation criteria)** **Long-term safety with comparator data (maximum 5 years after last patient randomized)**	**Final CSR**	**Planned for Quarter 4 of 2030**

Risk minimisation measures

Table 63 Description of routine risk minimisation measures by safety concern

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

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

Additional Risk Minimization 1:

Patient Card

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

Objectives:

- The objective of the Patient Card is to minimize the risk of CRS and ICANS by:
- Increasing patient awareness of CRS and ICANS
- Providing information on signs and symptoms of CRS and ICANS
- Alerting patients to promptly contact their HCPs/emergency care if they observe any of the signs or symptoms of CRS and ICANS
- Alerting HCPs treating the patient at any time, including in conditions of emergency, that the patient is using epcoritamab.

Rationale for the Additional Risk Minimization Activity:

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

Target Audience and Planned Distribution Path:

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

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

None.

Key messages of the additional risk minimization measure

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

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

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

The Patient Card will contain the following key messages:

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

The MAH does not propose new aRMM with the newly proposed FL indication, but the Patient card to inform of the risk of CRS and ICANS that is already in place for the BLCBL indication. It is agreed that no new safety concerns could be identified that would require additional risk minimization measures.

Other concern regarding the new posology (3-step SUD regimen) aimed to reduce the risk of CRS is pending for the next round in the clinical AR. Pending CHMP discussion, further measures may be required in later phase, however.

Overall conclusions on risk minimisation measures

The PRAC having considered the data submitted was of the opinion that the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication(s).

2.7. Update of the Product information

As a consequence of this new indication, sections 1, 2, 4.1, 4.2, 4.4, 4.8, 5.1, 5.2, 6.6 of the SmPC are being updated to reflect the addition of the new indication. The Package Leaflet has been updated accordingly. In addition, the labelling on the outer carton was also updated in light of the change of pharmaceutical form.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to the initial user test for Tepkinly EMEA/H/C/005985/0000. The bridging report submitted by the MAH has been found acceptable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Tepkinly is proposed as monotherapy for the treatment of adult patients with relapsed or refractory (R/R) follicular lymphoma (FL) after two or more lines of systemic therapy.

3.1.2. Available therapies and unmet medical need

Follicular lymphoma (FL) is the second most prevalent type of NHL, representing 25% of NHL cases, and is the most common type of iNHL (Swerdlow, 2008). For advanced disease, the most frequently used first-line therapies include an anti-CD20 (rituximab or obinutuzumab) combined with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) or bendamustine.

No universally accepted standard of care for the treatment of R/R FL currently exists due to the highly diverse clinical course of the disease. Treatment of R/R FL is influenced by previous treatment regimens, duration of remission, performance status, and other factors.

Approved treatment options for R/R FL in the European Union (EU) include a combination of chemotherapy (e.g., bendamustine, doxorubicin) and an anti-CD20 monoclonal antibody (rituximab or obinutuzumab), immunomodulatory agent (lenalidomide) in combination with rituximab (R2), radioimmunotherapy (ibritumomab tiuxetane), PI3K inhibitors (idelalisib and duvelisib), chimeric antigen receptor (CAR) T-cell therapies (tisa-cel, axi-cel and lico-cel), inhibitor of Bruton's tyrosine kinase (BTK) (zanubrutinib), and bispecific antibody (mosunetuzumab). None of the available

treatment options are considered curative. There is still an unmet medical need in this patient population.

3.1.3. Main clinical studies

The pivotal study for this application is the GCT3013-01 study, which is a first in human (FIH), phase 1/2, single arm trial that consists of a dose escalation part, an expansion part and an optimization part. The study includes subjects aged 18 years or older who had relapsed, progressive and/or refractory mature B-cell lymphoma. All patients in the expansion and optimization part of study GCT30313-01 had R/R disease to the last prior line therapy and were previously treated with at least 2 lines of systemic antineoplastic therapy including at least 1 anti-CD20 monoclonal antibody-containing therapy with an alkylating agent or lenalidomide. Subjects were premedicated with corticosteroids, antihistamines, and antipyretics prior to the first 4 doses of epcoritamab.

The iNHL cohort of the (ongoing) expansion part including FL Grade 1-3A is the pivotal study population. As of the data cutoff date of 21 April 2023 155 subjects have received at least 1 dose of epcoritamab. Of these 128 subjects were diagnosed with FL Grade 1-3A and 27 subjects with other iNHL subtypes (i.e., MZL and SLL).

The FL cohort of the optimization part of Study GCT3013-01, the FL cohort of GCT3013-04 study in Japanese subjects and a real world evidence study are presented as supportive studies. For safety data 2 safety pools were presented; R/R FL patients from Study GCT3013-01 and Study GCT3013-04 (N=151) and all B-NHL subjects in the escalation or expansion parts of these studies (N=449).

A new posology is introduced based on supportive efficacy and safety data from the FL cohort of the ongoing optimization part in Study GCT3013-01 (analyses in N=86 patients; cut-off date 08 January 2024). The FL cohort investigates an alternative 3 step SUD regimen; replacing the first full dose on D15 with a second intermediate dose of 3 mg in the approved posology. Also CRS management recommendations; adequate hydration and dexamethasone (instead of prednisolone) premedication in Cycle 1, repriming instructions and dose modifications for CRS were used.

3.2. Favourable effects

The primary endpoint ORR (CR + PR) in the FAS population (n=155) of the dose expansion cohort in the GCT3013-01 study, was 82.6%, with 97 subjects having a CR (62.6%). At the data cut of date, the median DOR for the FAS population using the primary definition was not reached (NR) (95% CI: 13.7, NR). In subjects with FL the ORR was 82.0% (95% CI: 74.3, 88.3), with 80 (62.5%) and 25 (19.5%) subjects achieving best responses of CR and PR, respectively. The estimated percentage of subjects remaining in response at 12 and 18 months was 68.7%, and 58.4%, respectively. The median follow up was 14.8 months (95% CI 10.0, 15.2). For patients with FL, the median DOR by secondary definition, i.e. not censoring for new anticancer therapy, was reached at 21.4 months (95% CI: 13.3, NR). The 12-month estimate of patients remaining in response, using secondary definition, was 66.5% (95% CI: 55.9, 75.2).

For FL patients who had a CR to epcoritamab treatment, median DOCR (primary definition) was not reached (NR) (95% CI: 21.4, NR), after a median DOCR follow-up of 14.8 months (95% CI 10.0, 15.2).

Updated efficacy data with DCO of 16 October 2023 were submitted which show an ORR based on IRC assessment determined by Lugano criteria of 82.8% (95% CI: 75.1, 88.9) in subjects with FL, with 81 (63.3%) and 25 (19.5%) subjects achieving best responses of CR and PR, respectively.

Updated DOR, for subjects with FL based on the primary definition (accounting for subsequent anti-lymphoma therapy and censoring DOR at the last adequate tumour assessment on or prior to the date of subsequent anti-lymphoma therapy) and secondary definition (not accounting for subsequent anti-lymphoma therapy) was respectively; 23.6 months [95% CI: 13.8, NR]) and 21.4 months [95% CI: 13.7, NR].

The ORR based on investigator assessment by Lugano criteria in subjects in Arm A of the FL optimization cohort as of the DCO of 08 January 2024 was 86.0% (95% CI: 76.9, 92.6), and the CR rate was 64.0% (95% CI: 52.9, 74.0). Among the subjects in Arm A of the FL optimization cohort who achieved PR or CR (n= 74), the median DOR follow-up was 2.8 months. The median DOR based on investigator assessment per primary definition was NR (95% CI: NR, NR).

3.3. Uncertainties and limitations about favourable effects

The single arm trial phase 1/2 design introduces inherent limitations. In the context of the CMA, data from randomized trials will be submitted as SOBs (see RMP and recommendations).

In order to be included in study GCT3013-01, patients needed to have documented CD20+ mature B-cell neoplasms by representative pathology report, and not necessarily at the time of screening. There are some indications that patients with low CD20 expression levels may respond less well to epcoritamab treatment. It is anticipated that additional data will be available post-authorisation through the SOBs (see Recommendations and RMP).

3.4. Unfavourable effects

The primary safety population (Safety Pool 01 R/R FL [N=129]) included all R/R FL subjects who were assigned to the 48 mg full dose and received at least 1 dose of epcoritamab in the escalation or expansion parts of Study GCT3013-01. A data cut-off date of 21 April 2023 was used for these safety populations.

- In the primary safety population the median duration of treatment was 8.3 months and 37.2% of subjects received at least 12 months of treatment.
- Almost all patients experienced any Grade TEAEs (N=127, 98.4%). The most frequently occurring TEAEs included CRS (66.7%), injection site reaction (36.4%), COVID-19 (31.0%), fatigue (30.2%), diarrhoea (26.4%), pyrexia (24.8%), neutropenia (20.2%).
- Grade ≤3 TEAEs were observed in 69.0% (N=89) of the patients. The most frequent Grade ≤3 TEAEs included neutropenia (17.1%), COVID-19 (10.9%), neutrophil count decreased (9.3%) and anaemia and lymphopenia (both 6.2%).
- Serious TEAEs were reported in 69.0% (N=89) of the patients. Most frequently reported were CRS (41.9%), COVID-19 (11.6%), COVID-19 pneumonia (7.8%), and pneumonia (5.4%).
- In total 13 (10.1%) fatal TEAEs were reported, including N=6 deaths (4.7%) due to COVID-19. None of the fatal TEAE were considered to be treatment-related.
- CRS, ICANS, and CTLS were considered to be AESIs; CRS was observed in 66.7% (N=86) of the patients, of which 40.3% had Grade 1, 24.8% had Grade 2 and 1.6% had Grade 3 CRS.

ICANS was seen in 6.2% of the patients (no Grade ≤ 3 events) and TLS was not observed in the primary safety population.

- Serious infections were observed in 40.3% (N =52) of the patients. The most frequently reported PTs were COVID-19 (11.6%), COVID 19 pneumonia (7.8%), and pneumonia (5.4%). Fatal infections were reported in 8 (6.2%) subjects (6 due to COVID -19 and one each due to pneumonia and pseudomonal sepsis organising pneumonia; not considered treatment-related). As of the DCO of 16 October 2023 the number of serious infections was 42.6%; the most frequently reported PTs (in ≥ 2% of subjects) were COVID-19 (14.0%), COVID-19 pneumonia (9.3%), pneumonia (6.2%), and Pneumocystis jirovecii pneumonia (2.3%). Grade 5 events of infection occurred in 9 (7%) patients, 6 (4.7%) of which were attributed to COVID-19 or COVID-19 pneumonia.
- Discontinuations due to TEAEs were reported in 18.6% (N=24) of the patients. The TEAEs included COVID-19 pneumonia (5.4%) and COVID-19 (3.9%).
- Safety data from the FL optimization cohort (N=86) with a median follow up of 5.7 months indicate that N=42 patients (48.8%) had a CRS event of which N=34 (39.5%) Grade 1 and N=8 (9.3%) Grade 2 CRS. The number of serious infections was 18.6%. The most common PTs were COVID-19 (4.7%), COVID-19 pneumonia (2.3%) and Urinary tract infection (2.3%). There were no fatal TEAEs observed.

Safety data from the primary safety population was largely comparable to the other safety pools. TEAEs in SOCs Infections and infestations (77.5% versus 64.4%), skin and subcutaneous tissues disorders (48.8% versus 37.6%), respiratory, thoracic and mediastinal disorders (43.4% versus 34.1%) were observed more frequently in Safety Pool 01 R/R FL patients compared to the All B-NHL safety pool.

3.5. Uncertainties and limitations about unfavourable effects

The safety database is based on single arm studies with no comparator and causality assessment of certain adverse events is challenging due to overlapping symptoms of the underlying diagnosis and toxicity from previous anticancer therapies. Long-term safety remains missing information.

The number of serious infections appears to be higher compared to other recently approved drugs for FL, however the number of fatal infections is comparable to recently approved drugs for FL. Whether this is due to epcoritamab, due to COVID-19 alone, due to the disease, due to prior treatments or may be due to the limitations of cross-study comparisons is uncertain. Literature indicates that patients with B-cell malignancies, particularly RR FL patients, age ≥ 70 years have a higher risk for COVID mortality compared to other lymphoma patients. In addition, literature studies provided by the MAH indicate that the number of deaths due to COVID-19 and the number of fatal infections in the pivotal study is comparable or lower compared to the other studies in FL patients conducted in the same time period as the pivotal study.

While a comparable safety profile is observed in the optimization cohort compared to the pivotal study cohort, the treatment and follow-up time in the optimization cohort is limited.

These uncertainties will be addressed by the submission of the results of post authorisation data and SOBs (see RMP and Recommendations).

3.6. Effects Table

Table 1. Effects Table for epcoritamab in adult patients with R/R FL after two or more lines of systemic therapy (data cut-off: 21 April 2023 and update DCO 16 October 2023).

Effect	Short description	Unit	Treatment	Uncertainties / Strength of evidence	References
ORR	Overall response rate (PR or CR by IRC)	% (N) (95% CI)	DCO 21.04.23 FAS 82.6% (128) FL1-3A 82.0% (105) FAS 82.6% (128) **FL1-3A 83% (106) (75.1, 88.9)**	Unc: Single arm trial, exploratory study SoE: Updated ORR per DCO 16 Oct 2023 in FL1-3A 82.8% (106)	GCT3013-01 study Data cutoff 16 October 2023
DOR	Duration of response	Months (95% CI)	FAS 21.4 (14.0, NR) FL1-3A NR (13.7, NR) Updated DOR per **DCO 16 Oct 2023** in FL1-3A 23.6 months (13.8, NR)	Unc: Short follow-up time Time between assessment is long after 24 weeks and even longer after 48 weeks of follow up SoE: support by updated data at later DCO and secondary endpoints	
CR	Complete response rate (by IRC)	% (N)	FAS 62.6% (97) FL1-3A (62.5% (80)	SoE: Updated CR per DCO 16 Oct 2023 in FL1-3A 63.3% (81)	
DOCR	Duration of complete response	Months (95% CI)	FAS and FL1-3a NR (21.4, NR)	SoE: Updated DOCR per DCO 16 Oct 2023 in FL1-3A NR (21.4, NR)	
Grade ⩽ 3 AE	Grade ⩽3 TEAE	% (N)	69.0% (N=89)	Unc: Long term exposure data is missing, but this may be acceptable considering the disease setting. The safety database is based on single arm studies with no comparator and causality assessment of certain adverse events is challenging due to overlapping symptoms of the underlying diagnosis and toxicity from previous anticancer therapies. SoE: None of the deaths were considered	GCT3013-01 study Data cutoff 16 October 2023
CRS	cytokine release syndrome	% (N)	49% (42/86)		
ICANS	Immune effector cell-associated neurotoxicity syndrome	% (N)	6.2% (N=8)		
TLS	Clinical tumour lysis syndrome	% (N)	0%		
Serious infections	Serious infections	% (N)	40.3% (N=52)		
Fatal TEAEs	Deaths due to TEAEs	% (N)	10.1% (N=13)		
Discont	Discontinuations due to TEAEs	% (N)	18.6% (N=24)		

Effect	Short description	Unit	Treatment	Uncertainties / Strength of evidence	References
				treatment – related.	

Abbreviations: AE= adverse event; CRS = cytokine release syndrome; FL = follicular lymphoma
Abbreviations: AE= adverse event; CRS = cytokine release syndrome; FL = follicular lymphoma; ICANS=immune effector cell-associated neurotoxicity syndrome; R/R = relapsed or refractory; TEAE = treatment-emergent adverse event TLS = clinical tumour lysis syndrome

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The reported overall response rate (CR+PR) after epcoritamab treatment are considered clinically relevant as supported by duration of response data. Updated DOR, with a DCO of 16 October 2023 for subjects with FL based on the primary definition (accounting for subsequent anti-lymphoma therapy and censoring DOR at the last adequate tumour assessment on or prior to the date of subsequent anti-lymphoma therapy) and secondary definition (not accounting for subsequent anti-lymphoma therapy) was respectively; 23.6 months [95% CI: 13.8, NR]) and 21.4 months [95% CI: 13.7, NR]. These DOR results are considered clinically relevant and sufficient to support the positive ORR results of epcoritamab in the GCT3013-01 iNHL expansion cohort.

The extent of exposure is considered acceptable considering the disease setting. No new safety signals are reported and safety data are largely comparable with the known safety profile for epcoritamab. The safety profile is also in line with what can be expected for a bispecific CD3/CD20-directed T-cell engager. Due to the MoA of activating T-cells CRS, ICANS, and CTLS are to be expected, as are cytopaenias and infections with bispecific antibodies. The safety profile seems to be acceptable considering the advanced nature of the disease and the pre-treated patient population under investigation.

A new posology and new CRS management recommendations were introduced based on a FL optimization cohort. Efficacy results in the optimization cohort appear similar to those in the expansion cohort. This would also be expected, given that the first full dose is only delayed by one week in the 3-step step-up dose (SUD) relative to the 2-step SUD. Further, similar B-cell depletion supports similar efficacy in FL subjects in the optimization cohort compared to the expansion cohort. IL-6 concentrations 24 h following the first full 48 mg dose were lower in FL patients in the optimization cohort compared to FL patients in the expansion cohort. A comparable safety profile is observed in the optimization cohort compared to the pivotal study cohort and no new safety concerns are raised, while a clinically relevant reduction in the number of (Grade 2) CRS events is observed for the optimization cohort compared to the expansion cohort. The addition of the 3-step SUD regimen, as well as CRS management recommendations to section 4.2 of the SmPC is therefore considered acceptable.

3.7.2. Balance of benefits and risks

The observed response rates translate into a clinically meaningful benefit as supported by duration of response. It is considered that the updated DOR results are clinically relevant and sufficient to support the positive ORR results of epcoritamab in the GCT3013-01 iNHL expansion cohort. The new posology is supported based on safety data and supportive pharmacokinetic and efficacy data.

The safety profile of epcoritamab is non-negligible, however it appears to be in line with the known safety profile for epcoritamab and in line with what can be expected for a bispecific CD3/CD20-directed T-cell engager.

The B/R balance in the indication of relapsed or refractory (R/R) follicular lymphoma (FL) after two or more lines of systemic therapy, is positive subject to the conditions as described in section 3.7.3.

3.7.3. Additional considerations on the benefit-risk balance

Conditional marketing authorisation

Tepkinly remains conditionally approved. Since comprehensive data on the product for the extension of indication to R/R FL after two or more lines of systemic therapy are not yet available, a conditional marketing authorisation was also proposed.

This extension of indication 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. It is considered that the new indication for epcoritamab fulfils the requirements for a conditional marketing authorisation:

- **The benefit-risk balance of epcoritamab is positive.**
- **The MAH will be able to provide comprehensive data**.

  The MAH will submit results from the confirmatory study M20-638, a phase 3, open-label study of epcoritamab in combination with R2 compared to R2 in subjects with RR FL. The adequacy of the Phase 3 Study M20-638 to fulfil the requirements to serve as a confirmatory study was previously discussed during the scientific advice that had been received on 15th Sep 2022 (EMA/SA/0000095173). Primary endpoint for the study is PFS and main secondary outcome measures are percentage of participants achieving CR, OS, and percentage of participants achieving MRD negativity. The planned completion date (Last Subject Last Visit) is in June 2030. As study recruitment is already started, given the number of participating study sites and the currently enrolled patients, completion of the study might be expected within a reasonable time frame. The final CSR will be submitted Q4 2030.

  In addition, the final CSR, including final efficacy and safety data for FL patients of both the iNHL expansion cohort and the FL optimization cohort of study the GCT3013-01 will be provided by mid-2028 and end of September 2029 respectively.

  In conclusion, it is likely that the MAH will be able to provide comprehensive data.

- **Epcoritamab fulfills an unmet medical need** for patients with R/R FL lymphoma.

  To justify the MTA, the MAH provided an inter-trial comparison of efficacy and safety data. Study results for epcoritamab were compared with study results of patients treated with R2 (rituximab+lenalidomide), BR (bendamustine and rituximab), obinutuzumab (Gazyvaro), ibritumomab (Zevalin), idelalisib (Zydelig), duvelisib (Copiktra), zanubrutinib (Brukinsa) in combination with obinutuzumab, axi-cel (Yescarta), tisa-cell (Kymriah) and mosunetuzumab (Lumsumio). Of these products Gazyvaro, Zydelig, Copiktra, Brukinsa, Yescarta, Kymriah, and Breyanzi have a full MA.

  Limitations associated with inter-trial comparisons should be noted, particularly when there are differences in study population and differences in methods to measure response duration.

Nevertheless, results indicate that ORR for epcoritamab, was comparable or higher to R2, BR, obinutuzumab, ibritumomab, idelalisib, duvelisib, zanubrutinib+obinutuzumab, and mosunetuzumab, suggesting as least a similar anti-tumour activity of epcoritamab as these agents. In addition, for all these agents except mosunetuzumab that is approved as CMA, CR for epcoritamab, was substantially higher (at least 20% higher), which might be considered a benefit justifying a MTA over these approved therapies. Mosunetuzumab (Lumsumio) is currently approved under a CMA. In line with Section 4.1.2 c) of the 'Guideline on the scientific application and the practical arrangements necessary to implement Commission Regulation (EC) No 507/2006 on the conditional marketing authorisation for medicinal products for human use falling within the scope of Regulation (EC) No 726/2004', the inter-trial comparison suggests that epcoritamab can be regarded as addressing the existing unmet medical need to a similar or greater extent than what is understood for the already conditionally authorised product Lunsumio.

Lower ORR and CCR were reported for epcoritamab in comparison to axi-cel and tisa-cel, however an advantage of epcoritamab versus the CAR-T cell therapies, is that epcoritamab is immediately available (off-the shelf) hence provided a major contribution to patient care. This is considered an MTA over the CAR-T cell therapies, including liso-cel.

- The benefits to public health of the immediate availability of epcoritamab outweigh the risks inherent in the fact that additional data are still required.

  The reported overall response rate (CR+PR) after epcoritamab treatment are considered clinically relevant when supported by duration of response data. Updated DOR, based on the primary definition was 23.6 months and based on secondary definition (not accounting for subsequent anti-lymphoma therapy) was 21.4 months [95% CI: 13.7, NR]. These results are considered clinically relevant and sufficient to support a clinically meaningful benefit of epcoritamab. Considering that the safety aspects appear to be in line with the known safety profile for epcoritamab and no new issues have been identified, in overall the benefits to the patients of the immediate availability of epcoritamab in the FL indication outweigh the risks associated with the fact that data from confirmatory are awaited.

3.8. Conclusions

The overall B/R of Tepkinly for the treatment of adult patients with relapsed or refractory (R/R) follicular lymphoma (FL) after two or more lines of systemic therapy is positive subject to the specific obligations and conditions stated in section 'Recommendations' in order to obtain further clinical data and generate a comprehensive clinical data set.

The following measures are considered necessary to address issues related to efficacy and safety:

- In order to confirm the safety and efficacy of epcoritamab in the treatment of R/R FL after two or more lines of systemic therapy, the pivotal iNHL expansion cohort of Study GCT3013-01 and the FL optimisation cohort of Study GCT3013-01 should be submitted
  - Final CSRs for the pivotal iNHL expansion cohort – due date: Q2/2028
  - Final CSR for the FL optimisation cohort - due date: Q3 2029.
- In order to confirm the benefit of epcoritamab in R/R FL, the MAH is conducting a Phase 3 study (study M20-638), to evaluate the safety and efficacy of epcoritamab in combination with R2 compared to R2 alone in subjects with R/R FL after at least one prior anti-CD20 containing

chemoimmunotherapy regimen. The final CSR will be submitted. Final CSR – due date: Q4 2030.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change subject to the following conditions:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, IIIA, IIIB and A

Extension of indication to include treatment of adult patients with relapsed or refractory (R/R) follicular lymphoma (FL) after two or more lines of systemic therapy for TEPKINLY, based on results from the indolent Non-Hodgkins Lymphoma (iNHL) expansion cohort of Study GCT3013-01, the First In Human (FIH) Phase 1/2 study in R/R B-NHL, with key supportive data from the Phase 1b/2 Study GCT3013-04 in Japanese subjects. Study GCT3013-01 is an ongoing global, single-arm, Phase 1/2 study designed to evaluate epcoritamab as monotherapy in R/R B-NHL. As a consequence, sections 1, 3, 4.1, 4.2, 4.4, 4.8, 5.1, 5.2, 6.3, 6.4, 6.5 and 6.6 of the SmPC are updated. The Package Leaflet and Labelling are updated in accordance. Annex A is updated to clarify the pharmaceutical form for the 4mg/0.8ml strength. Version 2.2 of the RMP has also been submitted. In addition, the MAH took the opportunity to introduce minor changes to the PI.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I, IIIA, IIIB and A and to the Risk Management Plan are recommended.

This recommendation is subject to the following updated conditions:

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 FL after two or more lines of systemic therapy, the pivotal iNHL expansion cohort of Study GCT3013-01 and the FL optimisation cohort of Study GCT3013-01 should be submitted - Final CSRs for the pivotal iNHL expansion cohort – due date: Q2/2028 - Final CSR for the FL optimisation cohort - due date: Q3 2029.	Q2/2028 Q3/2029
In order to confirm the benefit of epcoritamab in R/R FL, the MAH is conducting a Phase 3 study (study M20-638), to evaluate the safety and efficacy of epcoritamab in combination with R2 compared to R2 alone in subjects with R/R FL	Q4/2030

Description	Due date
after at least one prior anti-CD20 containing chemoimmunotherapy regimen. The final CSR will be submitted. Final CSR – due date: Q4 2030.	

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Tepkinly is not similar to Yescarta, Gazyvaro, Kymriah and Lunsumio within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000 (see appendix 1).

Additional market protection

Furthermore, the CHMP reviewed the data submitted by the MAH, taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004, and does not consider that the new therapeutic indication brings significant clinical benefit in comparison with existing therapies (see appendix 2).

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Product Name-H-C-Product Number-II-Var.No'