CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761324Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA/BLA Multi-disciplinary Review and Evaluation

Disclaimer: In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant, which do not necessarily reflect the positions of the FDA.

Application Type	Original Biologic License Application
Application Number(s)	BLA 761324
Priority or Standard	Priority
Submit Date(s)	September 21, 2023
Received Date(s)	September 21, 2023
PDUFA Goal Date	May 21, 2023
Division/Office	Division of Hematologic Malignancies II
Review Completion Date	May 19, 2023
Established Name	Epcoritamab
(Proposed) Trade Name	Epkinly
Pharmacologic Class	CD20-directed CD3 T-cell engaging bispecific antibody
Applicant	Genmab US, Inc.
Formulation(s)	Injection
Dosing Regimen	Injection: 4 mg/0.8 mL Injection: 48 mg/0.8 mL
Applicant Proposed Indication(s)/Population(s)	(b) (4)
Recommendation on Regulatory Action	Accelerated Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), not otherwise specified, including DLBCL arising from indolent lymphoma, and high-grade B-cell lymphoma, after two or more lines of systemic therapy

Table of Contents

Table of Tables

Table of Figures

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OPQ=Office of Pharmaceutical Quality
OBP= Office of Biotechnology Products
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology

Disclaimer: In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

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Glossary

ADA	anti-drug antibody
ADCC	antibody-dependent cellular cytotoxicity
ADCP	antibody-dependent cellular phagocytosis
ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aNHL	aggressive B-cell non-Hodgkin lymphoma
aPTT	activated partial thromboplastin time
ASCT	autologous stem cell transplant
ASTCT	American Society for Transplantation and Cellular Therapy
AUC	area under the concentration-time curve
$AUC_{0\text{-}28d}$	area under the concentration-time curve from time zero to time t=28 days
AUC_{inf}	area under the concentration-time curve to the time infinity
BEAM	carmustine, etoposide, gemcitabine, and dexamethasone
BIMO	Bioresearch Monitoring
BLA	Biologics License Application
BLQ	below the limit of quantification
B-NHL	B-cell non-Hodgkin lymphoma
BR	bendamustine and rituximab
bsAb	bispecific antibody
C1D1	Cycle 1 Day 1
C1D8	Cycle 1 Day 8
C1D15	Cycle 1 Day 15
C1D22	Cycle 1 Day 22
CAR T	chimeric antigen receptor T-(cell)
CD	cluster of differentiation
CDC	complement-dependent cytotoxicity
CDX	cell line-derived xenograft
CI	confidence interval
CLIPPERS	chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids
C_{max}	maximum concentration
CMC	chemistry, manufacturing, and control
CNS	central nervous system

COVID-19	coronavirus disease 2019
CR	complete response
CRO	Contract Research Organization
CRS	cytokine release syndrome
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor DNA
CTLS	clinical tumor lysis syndrome
CV%	coefficient of variation
DH	double-hit
DHAP	dexamethasone, cytarabine, and cisplatin
DLBCL	diffuse large B-cell lymphoma
DOCR	duration of complete response
DOR	duration of response
EC_{50}	concentration that induces 50% of the maximal response
ECG	electrocardiogram
eCRF	electronic case report form
ECOG	Eastern Cooperative Oncology Group
eCTD	electric Common Technical Document
eGFR	estimated glomerular filtration rate
EOP1	end of phase 1
E-R	exposure-response
FAS	full analysis set
FcRn	Fc receptor (neonatal)
FDA	Food and Drug Administration
FIH	first-in-human
FISH	fluorescence in situ hybridization
FITC	fluorescein isothiocyanate
FL	follicular lymphoma
GCP	Good Clinical Practice
G-CSF	granulocyte colony stimulating factor
GFR	glomerular filtration rate
GLP	Good Laboratory Practice
HCP	health care provider
HDT	high-dose therapy
HEK	human embryonic kidney
HGBCL	high grade B-cell lymphoma
HIS	humanized immune system
HSCT	hematopoietic stem cell transplantation
ICANS	immune effector cell-associated neurotoxicity syndrome
ICE	immune effector cell-associated encephalopathy assessment tool

ICH	International Conference on Harmonization
IFN-γ	interferon-gamma
IgG1	immunoglobulin G1
IL	interleukin
IND	investigational new drug
iNHL	indolent B-cell non-Hodgkin lymphoma
INR	international normalized ratio
IPI	international prognostic index
iPSP	initial pediatric study plan
IRC	Independent Review Committee
IV	intravenous(ly)
LBCL	large B-cell lymphoma
LDH	lactate dehydrogenase
LFT	live function test
mAb	monoclonal antibody
MCL	mantle cell lymphoma
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MOA	mechanism of action
MRD	minimal residual disease
mRES	modified response evaluable set
MZL	marginal zone lymphoma
NCI	National Cancer Institute
NCCN	National Comprehensive Cancer Network
NDA	New Drug Application
NHL	non-Hodgkin lymphoma
NOS	not otherwise specified
NR	not reached
ORR	overall response rate
OS	overall survival
PD	progressive disease
PDX	patient-derived xenograft
PFS	progression-free survival
PK	Pharmacokinetic(s)
PBMC	peripheral blood mononuclear cell
PMBCL	primary mediastinal B-cell lymphoma
PMDA	Pharmaceuticals and Medical Devices Agency
PML	progressive multifocal leukoencephalopathy
popPK	population pharmacokinetics
PR	partial response
PRO	patient-reported outcome

PT	preferred term
Q2W	once every 2 weeks
Q4W	once every 4 weeks
QSS	quasi-steady-state
QTcF	QT intervals corrected using Fridericia's formula
QW	once weekly
RDI	relative dose intensity
RES	response evaluable set
R-GemOx	rituximab, gemcitabine, and oxaliplatin
RP2D	recommended phase 2 dose
R/R	relapsed or refractory
RSE%	relative standard error
SAE	serious adverse event
SC	subcutaneous(ly)
SCT	stem cell transplant
SD	stable disease
SD	standard deviation
SEER	Surveillance, Epidemiology, and End Results Program
SLL	small lymphocytic lymphoma
SOC	system organ class
SPD	sum of the product of the diameters
TEAE	treatment-emergent adverse event
TH	triple-hit
TK	toxicokinetic
T_{max}	time to reach maximum concentration
TMDD	target-mediated drug disposition
TNF-α	tumor necrosis factor-alpha
TOI	trial outcome index
TTCR	time to complete response
TTNT	time to next anti-lymphoma therapy
TTR	time to response
US	United States
VAS	visual analog subscale
WHO	World Health Organization
WOE	weight of evidence

1 Executive Summary

1.1. Product Introduction

Product: Epcoritamab (EPKINLY)

Pharmacologic Class: Bispecific CD20-directed CD3 T-cell engager.

Proposed indication: (b) (4)

Dosing Regimen: The recommended dosage of epcoritamab is the following, where each cycle is 28 days in duration:

- Cycle 1: 0.16mg on Day 1, 0.8 mg on Day 8, 48 mg on Day 15 and Day 22 (b) (4)

1.2. Conclusions on the Substantial Evidence of Effectiveness

The FDA review team recommends accelerated approval of epcoritamab for the following indication:

Epcoritamab is a bispecific CD20-direced CD3 T-cell engager indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), not otherwise specified, including DLBCL arising from indolent lymphoma, and high-grade B-cell lymphoma, after two or more lines of systemic therapy.

This recommendation is based on the efficacy of epcoritamab from the pivotal Study GCT3013-01, an open-label, multi-cohort, single-arm trial that included an expansion cohort of 157 adult patients with relapsed or refractory large B-cell lymphoma who had received at least two prior lines of systemic therapies, including an anti-CD20 monoclonal antibody.

Patients received epcoritamab subcutaneously in 28-day cycles, at step-up dosing in Cycle 1 (0.16 mg on Day 1, 0.8 mg on Day 8, and 48 mg on Day 15 and Day 22), 48 mg weekly in Cycles 2-4, 48 mg every other week in Cycles 5-9, and 48 mg every four weeks from Cycles 10 onwards. Epcoritamab was administered until progressive disease or unacceptable toxicity.

Among the 157 patients with relapsed or refractory LBCL, the median age was 64 years (range: 20 to 83 years), 49% were 65 years of age or older, 60% were male, 61% were White, 19% were Asian, 0.6% were Native Hawaiian or Pacific Islander and none were Black or African American, or Hispanic or Latino. A total of 75% of patients had Stage III-IV disease, and 97% of patients had an ECOG performance status of 0 or 1. The patient population was heavily pretreated with a median number of prior therapies of 3 (range: 2 to 11), with 29% receiving 2 prior therapies, 32% receiving 3 prior therapies, and 39% receiving more than 3 prior therapies. Sixty-one percent of patients had primary refractory disease.

All patients had received prior anti-CD20 antibody therapy with or without an alkylating agent. In addition, most patients (98%) had received anthracycline-containing regimens. Consistent with the 3 median lines of therapy, patients had been exposed to several other therapies with 4% of patients having received prior anti-CD19 based therapy, 11% prior polatuzumab vedotin, 39% prior CAR-T therapy, and 20% prior autologous stem cell transplant.

Efficacy was established on the basis of objective response rate (ORR) and duration of response (DOR) as assessed by an independent review committee (IRC) according to Lugano Criteria (Cheson 2014). For the expansion cohort of 157 patients with R/R LBCL, the ORR rate as assessed by the IRC was 63% (95% CI: 55, 71), with 39% achieving a complete response (95% CI: 31, 47). The median DOR per Kaplan-Meier method was 15.5 months with a median DOR follow-up of 9.8 months.

In this population, the overall response rate of 63% with durability and a tolerable safety profile constitutes a meaningful clinical benefit. To support accelerated approval, the efficacy data are considered in the context of available therapy for patients with relapsed or refractory large B-cell lymphoma in the 3rd line setting and beyond. Available therapy includes chemoimmunotherapy options such as bendamustine plus rituximab (BR), gemcitabine or gemcitabine and oxaliplatin (GemOx) with or without rituximab. Additionally, polatuzumab vedotin plus BR or CAR T-cell therapy are available therapies in this setting. In the 3rd line setting and beyond, the ORRs for the chemoimmunotherapy options range from 25% to 38% with associated durability. Polatuzumab vedotin in combination with BR demonstrated an ORR of 63% with durability. Treatment with CAR T-cell therapy options yield high overall response rates and associated durability ranging from 50-73% and median DORs between 9.2 months and 16.7 months. However, CAR T-cell therapy represents a distinct therapeutic modality and these options may be limited due to eligibility and accessibility reasons. Of the 157 patients with R/R LBCL treated with epcoritamab, 71% had received 3 or more prior lines of systemic therapy, 39% received prior CAR T-cell therapy, 20% with prior autologous stem cell transplant, and 11% with prior polatuzumab vedotin. Therefore, the overall response of 63% with associated durability with epcoritamab provides data to support a clinically meaningful benefit in the context of available therapy for patients with relapsed or refractory large B-cell lymphoma in the 3rd line setting and beyond.

Given that the primary efficacy population consisted of 81% DLBCL (including 25% with DLBCL arising from indolent lymphoma), 13% high-grade B-cell lymphoma (HGBCL), and a limited number of patients with primary mediastinal B-cell lymphoma (PMBCL) and follicular lymphoma (FL) Grade 3B (3% each), (b) (4) (b) (4) the efficacy data for epcoritamab demonstrates substantial evidence of effectiveness in support of accelerated approval for the following indication:

- *Treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), not otherwise specified, including DLBCL arising from indolent lymphoma, and high-grade B-cell lymphoma, after two or more lines of systemic therapy*

1.3. Benefit-Risk Assessment (BRA)

Benefit-Risk Summary and Assessment

The benefit-risk assessment is favorable for epcoritamab, a bispecific CD20-directed CD3 T cell engager indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), not otherwise specified, including DLBCL arising from indolent lymphoma, and high-grade B-cell lymphoma, after two or more lines of systemic therapy

Efficacy:

Efficacy of epcoritamab is based on the results from the aggressive non-Hodgkin lymphoma (NHL) expansion cohort in Study GCT3013-01, an open-label, multicenter, multicohort study, which included 157 patients with relapsed or refractory large B-cell lymphoma who had received at least two prior therapies, including an anti-CD20 monoclonal antibody.

Patients received epcoritamab subcutaneously in 28-day cycles, at step-up dosing in Cycle 1 (0.16 mg on Day 1, 0.8 mg on Day 8, and 48 mg on Day 15 and Day 22), 48 mg weekly in Cycles 2-4, 48 mg every other week in Cycles 5-9, and 48 mg every four weeks from Cycles 10 onwards. Epcoritamab was administered until progressive disease or unacceptable toxicity.

Efficacy was established on the basis of objective response rate and duration of response as assessed by an independent review committee according to Lugano criteria (Cheson et al, 2014). Among the 157 patients, the ORR per IRC was 63% (95% CI: 55, 71), with 39% achieving a complete response (95% CI: 31, 47). With a median follow-up for DOR of 9.8 months, the estimated median DOR was 15.5 months (95% CI: 9.7, not reached). Of the 99 responders, 61% remained in response at 9 months.

Safety:

The safety profile of epcoritamab was primarily supported by analysis of 157 patients with R/R LBCL that received the recommended dose and regimen. The median duration of treatment was 5 cycles (range 1 to 20), with 69% exposed for at least 9 cycles. The most common adverse events (≥20%) were cytokine release syndrome (CRS, 51%), fatigue (29%), administration-related reactions (28%), musculoskeletal pain (28%), fever (24%), abdominal pain (23%), diarrhea (20%), and nausea (20%). The most common Grade 3 to 4 laboratory abnormalities (≥ 10%) were decreased lymphocyte count (77%), decreased neutrophil count (32%), decreased leukocyte count (22%), decreased hemoglobin (12%), and

decreased platelet count (12%). Serious adverse events occurred in 57%, most often due to CRS (29%), sepsis (9%), pleural effusion (5%), 3% each of COVID-19, febrile neutropenia, fever, immune effector-cell associated neurotoxicity syndrome (ICANS), renal insufficiency and urinary tract infection, and 2% each of cellulitis, pneumonia, and upper respiratory tract infection. Adverse events leading to treatment interruption occurred in 34%, most often due to CRS, neutropenia, and infection. Adverse events leading to treatment discontinuation occurred in 8%, most often due to infection, particularly COVID-19. Thus, the primary safety issues identified with epcoritamab include CRS, ICANS, infections, and cytopenias.

Benefit-Risk:

Epcoritamab has an overall favorable benefit-risk in patients with relapsed or refractory large B-cell lymphoma, including DLBCL, not otherwise specific, DLBCL arising from indolent lymphoma and HGBCL after two or more lines of systemic therapy. In the 157 patients with relapsed or refractory LBCL enrolled in the GCT 3013-01 study, the median age was 64 years (range: 20 to 83 years), 49% were 65 years of age or older, 60% were male, 61% were White, 19% were Asian, 0.6% were Native Hawaiian or Pacific Islander and none were Black or African American, or Hispanic or Latino. A total of 75% of patients had Stage III-IV disease and 97% of patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. The median number of prior therapies was 3 (range: 2 to 11), with 29% receiving 2 prior therapies, 32% receiving 3 prior therapies, and 39% receiving more than 3 prior therapies.

In this population, the overall response rate of 63% with durability and a tolerable safety profile constitutes a meaningful clinical benefit and a favorable benefit-risk evaluation. To support accelerated approval, the efficacy data are considered in the context of available therapy for patients with relapsed or refractory large B-cell lymphoma in the 3rd line setting and beyond. Available therapy includes chemoimmunotherapy options such as bendamustine plus rituximab (BR), gemcitabine or gemcitabine and oxaliplatin (GemOx) with or without rituximab. Additionally, polatuzumab vedotin plus BR or CAR T-cell therapy are available therapies in this setting. In the 3rd line setting and beyond, the ORRs for the chemoimmunotherapy options range from 25% to 38% with associated durability. Polatuzumab vedotin in combination with BR demonstrated an ORR of 63% with durability. Treatment with CAR T-cell therapy options yield high overall response rates and associated durability ranging from 50-73% and median DORs between 9.2 months and 16.7 months. However, CAR T-cell therapy represents a distinct therapeutic modality and these options may be limited due to eligibility and accessibility reasons. Of the 157 patients with R/R LBCL treated with epcoritamab, 71% had received 3 or more prior lines of systemic therapy, 39% received prior CAR T-cell therapy, 20% with prior autologous stem cell transplant, and 11% with prior polatuzumab vedotin. Therefore, the overall response of 63% with associated durability with epcoritamab provides data to support a clinically meaningful benefit in the context of available therapy for patients with relapsed or refractory large B-cell lymphoma in the 3rd line setting and beyond.

To further support an accelerated approval, the Applicant has an ongoing randomized trial in patients with relapsed or refractory large B-cell lymphoma. Study GCT3013-05 is an open-label, randomized trial evaluating epcoritamab monotherapy to an investigator's choice of standard chemoimmunotherapy in 480 patients with relapsed or refractory large B-cell lymphoma. The primary endpoint is overall survival with secondary endpoints that include progression-free survival and response rate. As of March 30, 2023, 475 patients have been enrolled out of the planned 480 patients. The FDA considers this ongoing trial to be supportive of accelerated approval for the indication described below.

Given that the primary efficacy population consisted of 81% DLBCL (including 25% with DLBCL arising from indolent lymphoma), 13% high-grade B-cell lymphoma (HGBCL), and a limited number of patients with primary mediastinal B-cell lymphoma (PMBCL) and follicular lymphoma (FL) Grade 3B (3% each), (b) (4) (b) (4) the efficacy data for epcoritamab demonstrates substantial evidence of effectiveness in support of accelerated approval for the following indication:

- *Treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), not otherwise specified, including DLBCL arising from indolent lymphoma, and high-grade B-cell lymphoma, after two or more lines of systemic therapy*

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Often presenting at advanced stages at diagnosis, LBCL are aggressive, fast-growing B-cell lymphomas, which account for ~30% of all cases of non-Hodgkin's lymphoma. • Although some patients can be cured following front-line therapy, between 30-50% will relapse or be refractory. Durable remissions may be observed with second-line therapy, but relapse is common, and patients carry a progressively dismal prognosis following each subsequent line of therapy.	Large B-cell lymphoma is a serious and life-threatening disease.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	• Available treatment options for relapsed and refractory large B-cell lymphoma include chemoimmunotherapy regimens such as rituximab combined with either gemcitabine and oxaliplatin or with bendamustine. Patients may also be treated with polatuzumab plus bendamustine and rituximab. • Treatment of patients in the third-line setting and beyond may involve CAR T-cell therapy (axi-cel, liso-cel, tisa-cel), each of which has regular approval, or agents with accelerated approval such as loncastuximab, selinexor, or tafasitamab combined with lenalidomide. • Relapses still present despite these treatment options.	New treatments are needed for patients with relapsed or refractory large B-cell lymphoma.
Benefit	• Study GCT3013-01 was an open-label, multicenter, multi-cohort study that included an expansion cohort of 157 patients with relapsed or refractory large B-cell lymphoma who had received at least 2 prior systemic therapies. • Epcoritamab was administered subcutaneously in 28-day cycles as follows: step-up dosing in Cycle 1 (0.16 mg on Day 1, 0.8 mg on Day 8, and 48 mg on Day 15 and Day 22), 48 mg weekly in Cycles 2-4, 48 mg every other week in Cycles 5-9, and 48 mg every four weeks from Cycles 10 onwards. • Objective response rate (ORR) per independent review committee in the 157 patients with relapsed and refractory large B-cell lymphoma was 63% (95% CI: 55,71) with 39% achieving a complete remission. • With a median follow-up for duration of response (DOR) of 9.8 months, the median DOR was 15.5 months (95% CI: 9.7, not reached).	Based on overall response rate (ORR) with durability, epcoritamab has clinically meaningful activity in patients with relapsed or refractory diffusion large B-cell lymphoma (DLBCL) not otherwise specified, including arising from indolent lymphoma, and high-grade B-cell lymphoma who have received two or more lines of systemic therapy.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	• The primary safety analysis was evaluated for the 157 patients with relapsed or refractory large B-cell lymphoma in the expansion cohort of Study GCT3013-01. Supportive safety data was based on 374 patients, which included the primary 157 patients and consisted of relapsed or refractory aggressive or indolent non-Hodgkin lymphoma who were treated at the registrational regimen of epcoritamab in the pivotal study GCT3013-01 and the similar Japan-only Study GCT3013-04. • The median duration of treatment was 5 cycles. • The most common adverse events (≥20%) were cytokine release syndrome (CRS), fatigue, administration-related reactions, musculoskeletal pain, fever, abdominal pain, diarrhea, and nausea. • The most common Grade 3 to 4 laboratory abnormalities (≥10%) were decreased lymphocyte count, decreased neutrophil count, decreased leukocyte count, decreased hemoglobin, and decreased platelet count. • Fatal adverse events occurred in 4% of patients and Grade 3-4 adverse events occurred in 59% • The most common serious adverse events included cytokine release syndrome, sepsis, pleural effusion, COVID-19, febrile neutropenia, fever, immune effector-cell associated neurotoxicity syndrome (ICANS), renal insufficiency, and urinary tract infections. • Adverse events that led to treatment discontinuation occurred in 8% of patients, most often due to infection, particularly COVID-19. • The key safety concerns for epcoritamab are CRS, ICANS, infections, and cytopenias.	The safety profile of epcoritamab is acceptable in the intended population. The USPI includes a boxed warning for CRS and ICANS and warnings and precautions for infections, cytopenias, and embryo-fetal toxicity. The USPI includes toxicity management for CRS, ICANS, infections, cytopenias, and other hematologic and non-hematologic toxicities. The safe use of epcoritamab can be managed through labeling and routine clinical care.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

X	The patient experience data that was submitted as part of the application, include:				Section where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as			Section 8.1.2
			X	Patient reported outcome (PRO)	
			□	Observer reported outcome (ObsRO)	
			□	Clinician reported outcome (ClinRO)	
			□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)			
	□	Patient-focused drug development or other stakeholder meeting summary reports			[e.g., Section 2.1 Analysis of Condition]
	□	Observational survey studies designed to capture patient experience data			
	□	Natural history studies			
	□	Patient preference studies (e.g., submitted studies or scientific publications)			
	□	Other: (Please specify)			
□	Patient experience data that was not submitted in the application, but was considered in this review.				

X

Nicholas Richardson, DO, MPH
Cross-Disciplinary Team Leader

X

Nicole Sunseri, MD, PhD
Clinical Reviewer

2 Therapeutic Context

2.1. Analysis of Condition

The Applicant's Position:

LBCL is a fast growing, aggressive subtype of NHL with a median survival of less than 1 year if left untreated. DLBCL represents the majority (80%) of all cases of LBCL (Sehn and Salles, 2021; Swerdlow et al., 2016); the annual incidence of DLBCL is estimated to be 5.6 per 100,000 in the US (SEER,◦2022).

Other rarer, aggressive subtypes of LBCL that are generally treated with the same regimens as DLBCL include FL grade 3B, PMBCL, and HGBCL. The incidence of FL grade 3B and PMBCL is 0.26, and 0.04 per 100,000 per year, respectively (SEER, 2022; Scott et al, 2018; Yu et al, 2021).

Approximately 10% of patients with LBCL have a particularly aggressive, difficult to treat disease characterized by chromosomal rearrangements involving the MYC gene, accompanied by BCL2 and/or BCL6 translocation(s), that can be detected by FISH analysis . The 2016 revision of the WHO classification of lymphoid neoplasms (Swerdlow, 2016) included 2 new categories of LBCL based on the presence or absence of these genetic markers for aggressive disease:

- HGBCL with MYC and BCL2 and/or BCL6 rearrangements (ie, double-hit [DH] and triple-hit [TH] lymphomas) and
- HGBCL, NOS, which lack MYC and BCL2 and/or BCL6 rearrangements

While recent therapies have improved outcome measures for relapsed or refractory patients with this life-threatening disease, an unmet medical need still exists for additional therapies that can provide meaningful benefit (ie, improved response rates, less toxicity), particularly for those who have primary refractory disease and/or disease refractory to multiple lines of therapy (including CAR T-cell therapy), patients with disease transformed from indolent lymphomas or with double-hit/triple-hit (DH/TH) disease, and frail patients. As a result, there is a pressing need for novel, effective, and widely available treatment options.

The FDA's Assessment:

The FDA agrees with the Applicant's position. DLBCL represents the majority of all cases of LBCL, accounting for approximately 80% of cases. Using data from the US Surveillance, Epidemiology, and End Results (SEER) program, the age adjusted incidence rate based on 2016-2020 cases of DLBCL was 5.5 per 100,000 men and women per year. Rates were higher in men (6.6) among all races than among women (4.5). Among men, rates were highest in Hispanics (7.2), followed by Non-Hispanic Whites (6.7), Non-Hispanic Asian/Pacific Islanders (6.2), Non-Hispanic American Indian/Alaska Natives (5.4), and Non-Hispanic Blacks (5.0). Among women, the trend was similar with the highest rates among Hispanics (5.4), followed by Non-Hispanic Asian/Pacific Islander (4.6), Non-Hispanic Whites (4.5), Non-Hispanic American Indian/Alaska Natives (4.4), and Non-Hispanic Blacks (3.4). The FDA agrees with the Applicant that the other

subtypes of aggressive LBCL, which include FL Grade 3B, HGBCL, and PMBCL, are rarer than DLBCL. However, treatment of these rare subtypes is generally approached in the same manner as DLBCL.

2.2. Analysis of Current Treatment Options

For patients with R/R LBCL, standard therapy is salvage chemotherapy with or without rituximab, followed by HDT and ASCT (Philip et al., 1995). However, fewer than 50% of patients are candidates for ASCT, and for those who respond to initial salvage therapy and then proceed to ASCT, the overall cure rate is only 25% to 35% (Sehn and Salles, 2021). The prognosis for patients whose disease is refractory to immunochemotherapy or who relapse within 12 months after HDT-ASCT is extremely poor, with an ORR of 26%, a CR rate of 7% of the subsequent treatment, and median OS of approximately 6.3 months (Crump et al, 2017). More recent therapies have been approved in this setting; however, there is no consensus on standard of care and the unmet medical need remains high for these patients.
Therapies that are commonly used and/or approved by the FDA for the treatment of R/R LBCL after 2 or more prior lines of systemic therapy are highlighted Table 1.

Table 1: Applicant – Summary of Treatment Armamentarium Relevant to Proposed Indication

Product (s) Name	Relevant Indication	Year of Approval And Type of Approval *	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
R-GemOx [a]	R/R LBCL	N/A	Rituximab (375 mg/m2) was delivered intravenously on day 1, and gemcitabine (1,000 mg/m2) and oxaliplatin (100 mg/m2) were administrated intravenously on day 2, every two weeks and continued for up to eight cycles if at least a PR was obtained after four cycles	EOT ORR = 38% EOT CR rate = 33% n = 196	Hematological toxicity, which can lead to neutropenia episodes and hospitalizations. Peripheral sensory neuropathy, considered to be related to oxaliplatin treatment, occurred in 26% of patients but was often of mild intensity and reversible.	Data are from a retrospective analysis going back 15 years, during which standard of care has changed. Most (58%) subjects had received only 1 line of prior anti-lymphoma therapy, and 42% were refractory to the previous line. No subject had received CAR T-cell therapy prior to being enrolled.
BR[b]	R/R LBCL	N/A	Bendamustine 90 mg/m2 on days 1 and 2 of each cycle and rituximab 375 mg/m2 on day 1 of each cycle. Intravenous	ORR = 25% CR rate = 23% EOT ORR = 18% EOT CR rate = 18% n = 40	Hematological toxicity, including 3-4 cytopenias. GI disorders occurred frequently (diarrhea in 11 [28.2%] subjects, nausea in 16 [41.0%] subjects, and constipation in 8 [20.5%] subjects but were	Eligible patients were not candidates for HD-ASCT or had experienced prior ASCT treatment

Product (s) Name	Relevant Indication	Year of Approval And Type of Approval *	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
					most often Grade 1 or 2.	failure at study entry, and the study excluded patients who had transformed lymphoma. Patients had not received prior CAR T-cell therapy. Although not excluded from the trial, there were no patients enrolled with double hit/triple hit disease.
CAR T-cell Therapies						
Yescarta® (axi-cel)[c]	For the treatment of adult patients with R/R large B-cell lymphoma after two or more lines of systemic therapy, including DLBCL not otherwise specified, primary mediastinal large B-cell lymphoma, HGBCL,	18-Oct-2017 Regular approval	Target dose of 2 x 10^6 CAR-positive viable T cells per kg body weight, with a maximum of 2 x 10^8. Intravenous	ORR = 72% mDOR = 9.2 mo CR rate = 51% n = 101	The toxicity profile of CAR T-cell therapies includes high rates of ≥grade 3 CRS and neurological toxicities, including ICANS	Due to the long waiting period for CAR T-cell therapies, as well as the need for intense safety monitoring, this treatment modality is currently limited

Product (s) Name	Relevant Indication	Year of Approval And Type of Approval *	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
	and DLBCL arising from follicular lymphoma					to specialized tertiary centers and for patients who are fit enough and can withstand delays in receiving active treatment.
Kymriah® (tisa-cel)[d]	Adult patients with relapsed or R/R large B-cell lymphoma after two or more lines of systemic therapy including DLBCL not otherwise specified, HGBCL and DLBCL arising from follicular lymphoma	01-May-2018 Regular approval	For patients 50 kg or less: 0.2 to 5.0 x 10^6 CAR-positive viable T cells per kg body weight intravenously For patients above 50 kg: 0.1 to 2.5 x 10^6 CAR-positive viable T cells intravenously	ORR = 50% mDOR = NR CR rate = 32% n = 68		
Breyanzi® (liso-cel)[e]	For the treatment of adult patients with R/R large B-cell lymphoma after two or more lines of systemic therapy, including DLBCL not otherwise specified (including DLBCL arising from indolent lymphoma), HGBCL, PMBCL, and follicular lymphoma grade 3B	01-Feb-2021 Regular approval	50 to 100 x 10^6 CAR-positive viable T cells intravenously	ORR = 73% mDOR = 16.7 mo CR rate = 54% n = 192		
Other Therapies						
Polivy® (polatuzumab	In combination with bendamustine and a	20-Jun-2019	1.8 mg/kg as an intravenous infusion over 90 minutes	ORR = 63% ORR (EOT) =	Substantial toxicity. ADRs included peripheral	Eligible patients were not

Product (s) Name	Relevant Indication	Year of Approval And Type of Approval *	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
vedotin) + BR[b]	rituximab product is indicated for the treatment of adult patients with R/R DLBCL, not otherwise specified, after at least two prior therapies	Accelerated approval	every 21 days for 6 cycles in combination with bendamustine and a rituximab product.	45% mDOR = 12.6 mo CR rate = 50% CR rate (EOT) = 40% n = 40	neuropathy in 40% of patients (all grades) and ≥Grade 3 infections in 32%. Febrile neutropenia was reported in 13% of patients (all were ≥Grade 3), and ≥Grade 3 laboratory abnormalities reported as ADRs included neutropenia in 39%, thrombocytopenia in 23%, and anemia in 14%.	candidates for HD-ASCT or had experienced prior ASCT treatment failure at study entry, and the study excluded patients who had transformed lymphoma. Patients had not received prior CAR T-cell therapy. Although not excluded from the trial, there were no patients enrolled with double hit/triple hit disease.
Monjuvi® (tafasitamab) + lenalidomide[f]	In combination with lenalidomide, is indicated for the treatment of adult patients with R/R DLBCL) not otherwise specified, including DLBCL arising from	31-Jul-2020 Accelerated approval	12 mg/kg administered via intravenous infusion according to the following dosing schedule: Cycle 1: Days 1, 4, 8, 15 and 22 of the 28-day cycle. Cycles 2 and 3: Days 1, 8, 15 and 22 of each 28-day cycle.	ORR = 55% mDOR = 43.9 mo CR rate = 37% n = 71	Myelosuppression seen with lenalidomide. Grade 3 or higher neutropenia, febrile neutropenia, and thrombocytopenia was 48%, 12%, and 17%, respectively	Study included DLBCL patients who received 1, but no more than 3 previous systemic regimens. Study excluded

Product (s) Name	Relevant Indication	Year of Approval And Type of Approval *	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
	low grade lymphoma, and who are not eligible for ASCT		Cycle 4 and beyond: Days 1 and 15 of each 28-day cycle Administered with lenalidomide for a maximum of 12 cycles, after which continue Monjuvi as monotherapy			patients with primary mediastinal (thymic) large B-cell, primary refractory disease (including patients with relapse within 3 months), double hit/triple hit disease, previous CD19-directed therapy including CAR-T therapy, and prior AlloSCT.
Zylonta® (loncastuximab tesirine)[g]	For the treatment of adult patients with R/R large B-cell lymphoma after two or more lines of systemic therapy, including DLBCL not otherwise specified, DLBCL arising from low-grade lymphoma, and HGBCL	23-Apr-2021 Accelerated approval	0.15 mg/kg administered via intravenous infusion every 3 weeks for 2 cycles, then 0.075 mg/kg every 3 weeks for subsequent cycles	ORR = 48.3% mDOR = 10.3 mo CR rate = 24.1% n = 145	Most common (≥20%) adverse reactions, including laboratory abnormalities, are thrombocytopenia, increased gamma-glutamyltransferase, neutropenia, anemia, hyperglycemia, transaminase elevation, fatigue, hypoalbuminemia, rash, edema, nausea, and musculoskeletal pain	9% of patients received prior CAR T-cell therapy and 58% were refectory to last line of therapy. 43% of patients had received 2 prior lines of therapy, with the remainder

Product (s) Name	Relevant Indication	Year of Approval And Type of Approval *	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
						receiving 3 or more.
Xpovio® (Selinexor)[h]	For the treatment of adult patients with R/R DLBCL, not otherwise specified, including DLBCL arising from follicular lymphoma, after at least 2 lines of systemic therapy	20-Jun-2020 Accelerated approval	60 mg taken orally on Days 1 and 3 of each week until disease progression or unacceptable toxicity Oral	ORR = 29% mDOR = 9.3 mo CR rate = 13% n = 134	ADRs included ≥Grade 3 fatigue in 15% of patients. ≥Grade 3 laboratory abnormalities included platelet count decrease (49%), neutrophil count decrease (31%), and hemoglobin decrease (25%).	Eligible patients were not candidates for ASCT, and the study required a minimum of 60 days since last systemic therapy, with a minimum of 98 days in patients with refractory disease (defined as less than PR) to last systemic therapy. Subjects had not received prior CAR T-cell therapy.

Abbreviations: AA = accelerated approval; ADC = antibody drug-conjugate; ASCT = autologous stem cell transplant; BR = bendamustine + rituximab; CAR = chimeric antigen receptor; CR= complete response; DLBCL = diffuse large B-cell lymphoma; DOR = duration of response; EOT = end of treatment; HGBCL = high grade B-cell lymphoma; IRC = Independent Review Committee; mAb = monoclonal antibody; mDOR = median duration of response; mo = months; NR = not reached; PMBCL = primary mediastinal large B-cell lymphoma; ORR = overall response rate; R/R = relapsed or refractory; TA = traditional approval; US PI = United States Prescribing Information.

a Source: (Cazelles et al., 2021). ORR and CR were reported as end of treatment, according to IWG response criteria (Cheson et al., 2007).

b Polivy US PI. BR was used as a comparator in the pivotal study GO29365. Efficacy was based on CR at end of treatment and DOR as determined by IRC by modified Lugano response criteria (Cheson et al., 2014).

c Yescarta US PI. Efficacy was based on CR and DOR as determined by IRC based on Lugano response criteria (Cheson et al., 2007).

d Kymriah US PI. Efficacy was based on CR and DOR as determined by IRC based on Lugano response criteria (Cheson et al., 2014).
e Breyanzi US PI. Efficacy was based on CR and DOR as determined by IRC using Lugano response criteria (Cheson et al., 2014).
f Monjuvi US PI. Efficacy was based on best ORR as assessed by IRC using the IWG Response Criteria (Cheson et al., 2007).
g Zynlonta US PI. Efficacy was established on the basis of ORR as assessed by IRC using Lugano response criteria (Cheson et al., 2014).
h Xpovio US PI. Efficacy was based on ORR and DOR by IRC using Lugano response criteria (Cheson et al., 2014).

The Applicant's Position:

While these recent advances have improved some outcome measures, there is no cure for patients with R/R LBCL. With each successive line of therapy, patients with R/R disease experience decreased response rates and shortened DOR. Some patients will no longer be sensitive to, or eligible for, available treatments. Outcomes remain poor for patients who do not respond to or relapse after CAR T-cell therapy, who are ineligible for HDT and ASCT and, particularly, for those patients who are elderly, have primary refractory disease, have disease transformed from indolent lymphomas, and/or have DH/TH disease.

The FDA's Assessment:

In general, the FDA agrees with the Applicant's position with the exception that polatuzumab vedotin has regular approval, rather than accelerated approval, when used in combination with bendamustine and rituximab to treat adult patients with relapsed or refractory DLBCL not otherwise specified after at least two prior therapies. This approval was granted in April 2023.

Although many cases of aggressive LBCL may demonstrate durable responses and even be cured with standard front-line chemoimmunotherapy (i.e., R-CHOP), approximately 30-50% of patients relapse or are refractory. Second-line therapy involves high-dose chemotherapy followed by autologous stem cell rescue (ASCT). More than half of those transplant-eligible patients will either have resistant disease or will relapse following ASCT. Additional available therapy for patients with relapsed/refractory LBCL includes chemoimmunotherapy options such as bendamustine plus rituximab (BR), gemcitabine or gemcitabine and oxaliplatin (GemOx) with or without rituximab. In the 3rd line setting and beyond, the ORRs for the chemoimmunotherapy options range from 25% to 38% with associated durability. Additionally, polatuzumab vedotin plus BR or CAR T-cell therapy are available therapies in this setting. Polatuzumab vedotin in combination with BR demonstrated an ORR of 63% with durability. While CAR T-cell therapy options typically yield higher overall response rates and associated durability ranging from 50-73% and median DORs between 9.2 months and 16.7 months, these options represent a distinct therapeutic modality and these options may be limited due to eligibility and accessibility reasons. Other options in the relapsed/refractory treatment armamentarium employ novel mechanisms of action and have accelerated approval, which result in response rates ranging from 29%-55%, and include the following regimens: tafasitamab plus lenalidomide, loncastuximab tesirine, and selinexor.

Thus, despite recent advances for the treatment of patients with relapsed or refractory LBCL, including those agents with novel mechanisms of action as demonstrated by several with accelerated approval, a high unmet medical need continues to exist for those patients who have relapsed or refractory disease or are not eligible for transplant, suggesting a need to further improve the treatment outcomes with accessible, safe, and more effective therapy.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The Applicant's Position:
Epcoritamab has not been approved for marketing in any country worldwide.

The FDA's Assessment:
The FDA agrees with the Applicant's position.

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant's Position:
Epcoritamab is being developed as monotherapy for the treatment of LBCL after 2 or more prior lines of systemic therapy. A summary of key pre-submission regulatory interactions related to BLA 761324 are summarized in Table 2.

Table 2: Applicant – Key FDA Interactions

Date	Type of Health Authority Interaction	Key Topic
14 Aug 2017	US FDA Pre-IND Meeting (ref ID 4139176)	Nonclinical safety package to support the FIH trial design (GCT3013-01) and key elements of the FIH trial design.
18 May 2020	US FDA Type B EOP1 (ref ID 4613473)	Nonclinical safety package, GCT3013-01 and GCT3013-05 trial design and considerations for regulatory filing.
10 Sep 2020	US FDA Type B EOP1 CMC Meeting (ref ID 4666348)	Comparability and PPQ strategy for BI, DS, and DP
08 Dec 2021	US FDA Type C Pre-BLA (ref ID 4902421)	Feedback on the content and format of the proposed BLA.
09 May 2022	FDA Type C (ref ID 4985202)	Clinical Pharmacology meeting to discuss dose optimization strategy.
28 Jun 2022	US FDA Type B Pre-BLA (ref ID 5008101)	Clinical topline results and additional submission components for BLA.

Abbreviations: BE FAMHP = Federal Agency for Medicines and Health Products of Belgium; BI = biological intermediate; BLA = Biologics License Application; CHMP = Committee for Medicinal Products for Human Use; CMA = conditional marketing authorization; CMC = chemistry, manufacturing, and controls; DLBCL = diffuse large B-cell lymphoma; DP = drug product; DS = drug substance; EMA = European Medicines Agency; EOP1 = end of phase 1; EU = European Union; F2F = face to face; FDA = Food and Drug Administration; FIH = first-in-human; IND = investigational new drug; LBCL = large B-cell lymphoma; MHRA = Medicines and Healthcare products Regulatory Agency; PPQ = process performance qualification; PRAC = Pharmacovigilance Risk Assessment Committee; R/R = relapsed or refractory; UK = United Kingdom; US = United States; WRO = written response only.

The FDA's Assessment:
The FDA agrees with the Applicant's assessment.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

Clinical site inspections were requested for two clinical sites based on risk ranking in the BIMO clinical investigator site selection tool (CISST), numbers of enrolled patients, and prior inspectional history, along with inspection of the Applicant, Genmab US, Inc. The clinical sites included 1) Site # US02 – University of Michigan (Dr. Yasmin Karimi; Ann Arbor, MI), which enrolled 12 patients and 2) Site FR07 – Hospital Saint-Louis (Dr. Catherine Thieblemont; Paris, France), which enrolled 9 patients. For both clinical site inspections, no objectionable conditions or practices were identified, and no actions were indicated. Therefore, based on the clinical site inspections, the study data from the clinical sites were considered reliable. Additionally, the Applicant was inspected concerning its oversight of GCT3013-01. Based on the inspection, no objectionable conditions or practices were identified, and no actions were indicated. Thus, the Applicant's oversight of the clinical trial and the quality of conducting the study were determined to be adequate. The audited study data submitted to the Agency was deemed acceptable in support of the BLA application, in compliance with Good Clinical Practice.

4.2. Product Quality

Epcoritamab is bispecific CD20-directed CD3 T-cell engager. It is a humanized monoclonal anti-CD20xCD3 T-cell-dependent bispecific antibody of the immunoglobulin G1 (IgG1) isotype. Epcoritamab-bysp is produced in Chinese Hamster Ovary (CHO) cells by recombinant DNA technology. The approximate molecular weight is 149 kDa.

Epcoritamab-bysp injection is a sterile, preservative-free, clear to slightly opalescent, colorless to slightly yellow solution for subcutaneous use.

Each single-dose 4 mg/0.8 mL vial contains epcoritamab-bysp (4 mg), acetic acid (0.19 mg), polysorbate 80 (0.32 mg), sodium acetate (1.7 mg), sorbitol (21.9 mg) and Water for Injection, USP. The pH is 5.5.

Each single-dose 48 mg/0.8 mL vial contains epcoritamab-bysp (48 mg), acetic acid (0.19 mg), polysorbate 80 (0.32 mg), sodium acetate (1.7 mg), sorbitol (21.9 mg) and Water for Injection, USP. The pH is 5.5.

The Office of Pharmaceutical Quality recommends approval of epcoritamab-bysp manufactured by Genmab, Inc. for human use under the conditions specified in the package insert. The data submitted support the conclusion that the manufacture of epcoritamab-bysp is well-controlled and leads to a product that is pure and potent.

4.3. Clinical Microbiology

The microbiology product quality and sterility assurance data are adequate to support approval.

4.4. Devices and Companion Diagnostic Issues

Not applicable.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Epcoritamab (also referred to as GEN3013) is an IgG1-based bispecific antibody (bsAb) construct directed against CD3 and CD20. The CD3 receptor complex is expressed on the surface of T-cells. CD20 is expressed on the surface of normal B-cells and human B-lymphoma cells. The Applicant developed epcoritamab to promote the T-cell dependent elimination of CD20-expressing B-cell lymphoma cells. The indication is for the treatment of adult patients with relapsed or refractory large B-cell lymphoma (DLBCL), not otherwise specified, including DLBCL arising from indolent lymphoma, and high-grade B-cell lymphoma, after two or more lines of systemic therapy, and the intended route of administration is subcutaneous (SC) injection.

In in vitro studies, epcoritamab bound T-cells isolated from healthy human donors (K_D=4.73 nM); epcoritamab bound a cell line transfected with human CD20 and a Burkitt's lymphoma cell line with slightly lower affinity (K_D values of 2.47 nM and 10.40 nM, respectively). Epcoritamab simultaneously bound to CD3-expressing T-cells and CD20-expressing B-cells in the whole blood from healthy human donors, consistent with the purported cytolytic synapse mechanism of action (MOA).

Epcoritamab bound a transformed cynomolgus monkey T-cell line (K_D=1.8 nM) and a cell line transfected with cynomolgus monkey CD20 (K_D=2.80 nM); the affinity of epcoritamab to the human target antigens and the cynomolgus monkey orthologues was similar. Epcoritamab bound a cell line transfected with rabbit CD20 (K_D=6.93 nM), but did not bind cells expressing dog, pig, rat, or mouse CD20 under the conditions tested. The binding of epcoritamab to dog, rabbit, pig, rat, or mouse CD3 was not experimentally determined, but based on CD3 protein sequence alignments, epcoritamab is not expected to bind to CD3 in these species. The epcoritamab binding data indicates that among the species tested, the cynomolgus monkey is the only pharmacologically relevant species for toxicology studies.

Point mutations were introduced into the epcoritamab Fc region to abrogate Fcγ receptor binding and associated Fc-mediated effector functions; these mutations ensure that epcoritamab-mediated immune cell activation is dependent on the presence of CD20-expressing target cells. The inertness of the Fc region was confirmed in a series of in vitro binding and activity assays with epcoritamab or the parental anti-CD3 or anti-CD20 antibodies. Each of the antibodies demonstrated no Fcγ receptor binding and minimal or no C1q binding under the conditions tested. Epcoritamab and the parental anti-CD20 antibody both demonstrated minimal activity in an in vitro complement-dependent cytotoxicity (CDC) assay (7-30% of control IgG1). While antibody-dependent cellular cytotoxicity (ADCC) and antibody-

dependent cellular phagocytosis (ADCP) assays were not conducted, epcoritamab is not expected to induce these effector mechanisms given the absence of Fcγ receptor binding. The point mutations in the epcoritamab Fc region did not affect neonatal Fc receptor (FcRn) binding.

The functional activity of epcoritamab to induce T-cell activation and T-cell-mediated cytotoxicity was evaluated in a series of in vitro redirected lysis assays where CD3-expressing effector cells were co-incubated with CD20-expressing target cells. T-cell activation was measured in a cell-based reporter gene assay and by upregulation of activation markers as measured by flow cytometry. T-cell-mediated cytotoxicity was measured by intracellular release of ^{51}Cr and physical cellular characteristics as measured by flow cytometry. Epcoritamab induced concentration-dependent T-cell activation (EC_{50}=0.073–2.400 pM) and T-cell-mediated cytotoxicity (EC_{50}=0.260–4.251 pM) with activity only observed in the presence of CD20-expressing target cells. The potency of epcoritamab varied by assay conditions and readout, and there was no correlation between the target cell CD20 expression level and sensitivity to T-cell activation or cytotoxicity. The in vitro activities of epcoritamab were dependent on the binding to both CD3 and CD20 antigens and consistent with the induction of T-cell-mediated cytotoxicity towards CD20-expressing target cells. In separate in vitro studies with human whole blood, epcoritamab caused the release of cytokines.

The in vivo antitumor activity of epcoritamab was evaluated in various human lymphoma cell line-derived xenograft (CDX) mouse models and in one patient-derived xenograft (PDX) mouse model. In the CDX studies, immunodeficient mice were injected with lymphoma cell lines and human peripheral blood mononuclear cells (PBMC). Alternatively, immunodeficient mice were inoculated with $CD34^+$ progenitor cells, and once humanization was confirmed by flow cytometry, lymphoma cell lines were injected. In the prophylactic setting, epcoritamab treatment was initiated within 3 days of tumor cell injection, while in the established setting tumors were allowed to form (volume ~100 mm^3) prior to initiating epcoritamab treatment. In a late treatment study, the average tumor volume was ~677 mm^3 prior to initiating epcoritamab treatment. In the PDX model, immunodeficient mice that had been humanized by engraftment of $CD34^+$ progenitor cells as described above were injected with human diffuse large B-cell lymphoma (DLBCL) tumor biopsy fragments that had been passaged in mice; epcoritamab treatment was initiated when tumors were 100-200 mm^3 in volume.

In all xenograft studies, epcoritamab was administered intravenously (IV), but the dose levels and dosing regimens varied by study. In the CDX mouse models, epcoritamab conferred antitumor activity relative to vehicle- or control antibody-treated mice. Antitumor activity was observed in each of the prophylactic, established, and late treatment settings, but the relative antitumor activities could not be established due to the varied study designs and treatments. In the PDX model, epcoritamab conferred antitumor activity relative to control antibody-treated

mice. The antitumor activity in both the CDX and PDX models was accompanied by peripheral T-cell activation and B-cell depletion.

The toxicity and toxicokinetics (TK) of epcoritamab were evaluated in a 5-week toxicity study in cynomolgus monkeys. Monkeys were administered epcoritamab as a once weekly (QW x 5) IV infusion (0 [control], 0.01, 0.1, or 1 mg/kg), a single IV infusion (0.1 or 1 mg/kg), or a once monthly (Days 1 and 29) subcutaneous (SC) injection (0.1, 1, or 10 mg/kg). A 6-week recovery period evaluated the reversibility of the changes after repeated IV infusions at the high dose level.

One female (single IV infusion at 1 mg/kg) was prematurely sacrificed approximately 12.75 hours post dose due to adverse clinical signs (decreased activity, hunched posture, subdued and weak) that were associated with elevated cytokine levels. Similar clinical signs as well as vomiting, generalized reddened skin, and/or uncoordinated movements were observed in additional animals after IV and SC administration but resolved by 24 hours post dose. Significant increases in cytokines were observed after the first dose; cytokine levels were lower following SC administration relative to IV administration (at equivalent dose levels) and were lower after repeated doses. There were reversible changes in hematology (increase in total leukocyte and lymphocyte counts) and immunophenotyping (decrease in T-cells and B-cells) parameters, and correlating histopathology findings in various lymphoid tissues (decreased cellularity in the lymphoid follicles). Cytokine release, B-cell depletion, and decreased lymphoid cellularity in the lymphoid tissues are consistent with the expected pharmacology of epcoritamab. Following repeated IV doses of epcoritamab, anti-drug antibodies (ADAs) were observed in all animals at ≤0.1 mg/kg and in some animals at 1 mg/kg. Epcoritamab concentrations were low or non-quantifiable following the development of ADAs. ADA-positive animals were excluded from TK evaluations from the initial ADA-positive response onwards. Following repeated IV doses, the epcoritamab group mean systemic exposure (C_{max}, $AUC_{0\text{-}168h}$) increased in a greater than dose-proportional manner across the dose range in both males and females. Absolute bioavailability could only be reliably determined at 1 mg/kg; based on mean $AUC_{0\text{-}inf}$, bioavailability by the SC route was 85% and 49% in males and females, respectively.

Since epcoritamab exhibited a strong neutralizing ADA response in the 5-week repeat-dose toxicity study in cynomolgus monkeys, systemic exposure to epcoritamab would not have been maintained in a 3-month repeat-dose toxicity study. A 3-month repeat-dose toxicity study would not provide meaningful information and is not warranted to support a BLA. The ADAs observed in the toxicity study in cynomolgus monkeys are not predictive of potential immunogenicity in patients. Toxicology studies were not conducted in rodents due to the lack of epcoritamab binding in these species.

The Applicant provided a weight of evidence (WOE)-based approach for the assessment of

potential reproductive and developmental toxicity. Epcoritamab is a T-cell redirecting bsAb and causes T-cell activation and cytokine release in the presence of CD20-positive cells. CD20 is expressed on the surface of normal B-cells. Immune activation in the mother may adversely affect the maintenance of pregnancy. In addition, epcoritamab may cross the placenta to the developing fetus and cause immune activation, or B-cell depletion in infants from in utero exposure. Because of these adverse effects, effective contraception is recommended for female patients of reproductive potential while receiving epcoritamab and for 4 months after the last dose. The recommendation for the duration of contraception use is based on the FDA guidance "Oncology Pharmaceuticals: Reproductive Toxicity Testing and Labeling Recommendations".

There are no data on the presence of epcoritamab in human milk, the effects on the breastfed child, or on milk production. Epcoritamab is an IgG1-based bsAb and may be present in milk; a breastfed child may be exposed to epcoritamab via lactational transfer. Because of the potential for serious adverse events (SAEs) in the breastfed child, the product label for epcoritamab recommends women to avoid breastfeeding during treatment with epcoritamab and for 4 months after the last dose. The recommendation for the duration to avoid breastfeeding is based on five-times the mean half-life of the full human dose of epcoritamab (48 mg), rounded to 4 months.

Epcoritamab binds CD3 and CD20 and promotes the T-cell dependent elimination of CD20-expressing cells; the Established Pharmacologic Class of epcoritamab is “bispecific CD20-directed CD3 T-cell engager”.

The nonclinical pharmacology, TK, and toxicology data submitted to BLA 761324 are adequate to support the approval of epcoritamab for the proposed indication.

5.2.Referenced NDAs, BLAs, DMFs

The Applicant’s Position:
N/A

The FDA’s Assessment:
We agree that no other applications are being referenced to support the approval of BLA 761324.

5.3.Pharmacology

The Applicant’s Position:

Primary pharmacology

Epcoritamab (GEN3013, DuoBody®-CD3xCD20) is an IgG1 bispecific antibody recognizing the T-cell antigen CD3 and the B-cell antigen CD20.

Study# 3013-030, (eCTD location: 4.2.1.1), 3013-034 (eCTD location: 4.2.3.7.7):
Epcoritamab binds specifically and with high affinity to human and cynomolgus CD20 and CD3, which supports the use of cynomolgus monkeys as part of the nonclinical toxicology program.

Table 3: Applicant - Binding of epcoritamab to CD3 and CD20 (flow cytometry)

Human			Cynomolgus monkey		
	Average EC_{50}± SD			Average EC_{50}± SD	
Cells	**µg/mL**	**nM**	**Cells**	**µg/mL**	**nM**
Jurkat (n=11)	0.24 ±0.11	1.60 ± 0.73	**HSC-F (n=3)**	0.27 ± 0.12	1.8 ± 0.8
Primary T cells (n=7)	0.71 ± 0.37	4.73 ±2.47			
HEK293F-CD20 (n=3)	0.37 ± 0.20	2.47 ± 1.33	**HEK293F-CD20 (n=3)**	0.42 ± 0.15	2.80 ± 1.00
Daudi (n=8)	1.56 ± 1.90	10.40 ± 12.67			

Note: Binding of epcoritamab to CD3 on a human (Jurkat) and a cynomolgus monkey (HSC-F) T-cell line, and on human primary T cells, and to CD20 on HEK293F cells transfected with CD20 of human or cynomolgus origin, and on a human cell line (Daudi) were determined by flow cytometry.

Epcoritamab is capable of simultaneous binding to CD3-expressing T cells (both CD4+ and CD8+) and CD20-expressing B cells, as determined by flow cytometry in whole blood samples.

Study# 3013-045 (eCTD location:4.2.1.1):
Epcoritamab has a silenced Fc region and does not induce T-cell activation through FcγR-dependent crosslinking of CD3. Due to its silenced Fc region, the capacity of epcoritamab to induce CDC is strongly reduced, with minimal CDC on CD20+ cells at clinically relevant antibody concentrations (1-10 µg/mL). Binding to FcRn is retained.

Study# 3013-032 (eCTD location: 4.2.1.1):
Epcoritamab induces T-cell activation and T-cell mediated cytotoxicity of CD20+ cells in in vitro preclinical studies.

Table 4: Applicant - Induction of T-cell-mediated cytotoxicity by epcoritamab

Cytotoxicity Assay	Effector Cells	Daudi Cells				Healthy Donor B Cells			
		E:T Ratio	EC_{50} [SD] in pg/mL	EC_{50} [SD] in pM	n Donors	E:T Ratio	EC_{50} [SD] in pg/mL	EC_{50} [SD] in pM	n Donors
^{51}Cr release	T cells	10:1	634 [1,165]	4.227 [7.769]	20	NA	NA	NA	NA
	CD4+ T cells	10:1	638 [604]	4.251 [4.029]	6	NA	NA	NA	NA
	CD8+ T cells	10:1	126 [119]	0.841 [0.792]	5	NA	NA	NA	NA
Flow cytometry	T cells	2:1	39 [22]	0.260 [0.147]	11	~5:1	474 [761]	3.160 [5.073]	5

Study# GMB3013-033, -073, -083 (eCTD location:4.2.1.1)

Epcoritamab showed anti-tumor activity in 3 different B-cell lymphoma xenograft models (CDX) and 1 DLBCL PDX model in humanized mice, in vivo. Anti-tumor activity was observed even when treatment was started at high tumor burden (500 mm^3) in a CDX model. Epcoritamab was administered IV.

Table 5: Applicant - Anti-tumor activity of epcoritamab in mouse models in vivo

Study#	Tumor model	Mice	Dose level	Results
GMB3013-033	Mixture of Raji-luc tumor cells and human PBMCs, SC	NOD/SCID mice;5-10 mice/group	0.005–0.5 mg/kg (single dose or Q1Wx2)	Epcoritamab effectively reduced growth of Raji Burkitt's lymphoma in a dose-dependent manner.
GMB3013-033	JEKO-1 tumor cells, SC, and human PBMCs, IP	NCG mice;10 mice/group	0.05–0.5 mg/kg (2Q1Wx5)	Epcoritamab (0.5 mg/kg) effectively reduced tumor growth and induced tumor regression of an established mantle-cell lymphoma (JEKO-1) xenograft.
GMB3013-033	Daudi-luc (IV), and Raji-luc (SC) tumor cells	BRGS-HIS mice;6-8 mice/group	1 mg/kg (2Q1Wx2) (Daudi) 0.1-1 mg/kg (2Q1Wx5) (Raji)	Epcoritamab effectively reduced growth of IV and SC inoculated Burkitt's lymphoma at all doses tested.
GMB3013-073	Raji-luc tumor cells, SC	NSG-HIS mice;9 mice/group	0.05–5 mg/kg (Q1Wx5) 5 mg/kg (single dose, late treatment group)	Epcoritamab effectively reduced growth of Raji Burkitt's lymphoma, also upon single-dose treatment of large (~500 mm^3) tumors, at the doses tested.
GMB3013-083	HuPrime lymphoma xenograft model LY2214 (DLBCL), SC	huNOG mice;9 mice/group	0.05–5 mg/kg (Q1Wx6)	Epcoritamab effectively reduced growth of DLBCL PDX at the highest dose (5 mg/kg).

The FDA's Assessment:

We agree with the Applicant's assessment of the primary pharmacology studies as described above, and have the following additional comments:

- Studies 3013-030 and 3013-034: Epcoritamab binding studies were conducted with human embryonic kidney (HEK) 293F cells transfected with human, cynomolgus monkey, dog, rabbit, pig, rat, or mouse CD20. Binding was analyzed by flow cytometry, and EC_{50} values for human and cynomolgus monkey CD20 are described in Table 3 presented by the Applicant. Epcoritamab did not bind dog, pig, rat, or mouse CD20 under the conditions tested. Epcoritamab bound rabbit CD20 with an EC_{50} value of 1.04 µg/mL (6.93 nM), an approximately three-fold lower affinity than for human or cynomolgus monkey CD20. The binding of epcoritamab to dog, rabbit, pig, rat, or mouse CD3 was not experimentally determined.
- Study 3013-032: T-cell activation was assessed with NFAT-Luc2 Jurkat reporter cells and by upregulation of CD69, CD25, and PD-1 on the cell surface of T-cells as measured by flow cytometry. In some flow cytometry studies, healthy human donor PBMCs were used as both a source of effector and target cells; in other studies, purified human T-cells were used as effector cells, and CD20-expressing lymphoma cell lines were used as target cells. Cytotoxicity was assessed by ^{51}Cr release or flow cytometry. Results of T-cell activation assays with the Daudi target cell line are described in Table 6. Results of cytotoxicity assays are described in Table 4 from the Applicant above. T-cell activation and cytotoxicity assays were conducted with twelve B-cell lymphoma target cell lines; there was no correlation between the target cell CD20 expression level and the average or maximal T-cell activation or sensitivity to cytotoxicity. No T-cell mediated cytotoxicity was observed with target cells lacking CD20, and no T-cell activation or T-cell mediated cytotoxicity was observed with control bsAbs that singly targeted CD3 or CD20.
- Studies 3013-033, 3013-073, and 3013-083: Epcoritamab demonstrated antitumor activity in both unestablished and established tumor models. In the studies with immunodeficient mice with humanized immune systems (HIS), antitumor activity correlated with a decrease in the number of $CD19^+$ B-cells and upregulation of CD69 or CD25 on T-cells in the peripheral blood.

Table 6: Induction of T-Cell Activation by Epcoritamab after Coincubation with Daudi Target Cells

Effector cell type	Average EC_{50} value for CD69 upregulation (% $CD69^+$)			Average EC_{50} value for CD25 upregulation (% $CD25^+$)			Average EC_{50} value for PD-1 upregulation (% $PD\text{-}1^+$)		
	ng/mL	pM	n	ng/mL	pM	n	ng/mL	pM	n
$CD4^+$ T-cells	0.011	0.073	10	0.021	0.140	11	0.068	0.453	10
$CD8^+$ T-cells	0.025	0.167	10	0.076	0.507	11	0.360	2.400	10

Secondary Pharmacology

The Applicant's Position:

Study# GMB3013-031, -055 (eCTD location:4.2.1.2)

In silico and in vitro analyses predicted low risk of clinical immunogenicity of the variable domains of the epcoritamab CD3-specific Fab arm and the Fc region, containing the silencing mutations and the DuoBody mutations. No immunogenicity studies were performed for the variable domain of the CD20-specific arm because this arm is fully human. No other secondary pharmacodynamic studies were conducted.

The FDA's Assessment:
We agree with the Applicant's assessment of the secondary pharmacology studies as described above.

Safety Pharmacology

The Applicant's Position:
No effect was observed on electrocardiogram (ECG), heart rate, and detailed clinical observations parameters evaluated as part of the general toxicology studies performed in cynomolgus monkeys with IV and SC administration of epcoritamab.

The FDA's Assessment:
We agree the cynomolgus monkey is a pharmacologically relevant nonclinical species to assess the safety pharmacology of epcoritamab, and we agree there were no epcoritamab-related ECG findings or respiratory clinical observations in the 5-week repeat-dose toxicity study. Clinical observations in monkeys suggestive of CNS effects included slightly uncoordinated movements after dosing on Day 1, the incidence of which increased with dose level. The incidence of uncoordinated movements correlated with decreased activity and hunched posture, and were considered potentially-related to elevated cytokine levels.

5.4.ADME/PK

The Applicant's Position:

Epcoritamab is a high molecular weight protein drug with biochemical characteristics of an endogenous IgG1 antibody and is expected to display similar patterns of distribution, metabolism, and excretion. Therefore, no specific ADME studies have been conducted.

The PK of epcoritamab was evaluated in cynomolgus monkeys as part of the nonclinical toxicology program (Single Dose Toxicology Study (b) (4) 529668 - eCTD section 4.2.3.1; Dose Range Finding Toxicology Study (b) (4) 501775 - eCTD section 4.2.3.2; GLP Toxicology Study (b) (4) 503484 - eCTD section 4.2.3.2). Plasma concentration vs time profiles were generally consistent with the respective IV (infusion) and SC (injection) dose routes. Epcoritamab displayed a clear pattern of target-mediated drug disposition, with faster clearance of drug at low doses compared with high doses.

Anti-drug antibody responses impacted exposure upon repeated IV administration in the lowest 2 dose groups in the GLP toxicology study. Exposures were sustained in most animals at the highest dose of 1 mg/kg. Accumulation ratios in AUCs of 1.8 and up to 3.5 were observed at Day 15 and Day 29, respectively, while no notable accumulation was seen in C_{max}. No meaningful differences in PK between male and female monkeys were observed.

While AUCs were comparable after IV and SC administration at the same dose level, indicating a high SC bioavailability, peak plasma exposures observed upon SC dosing were approximately a factor 10 lower compared to IV.

The average C_{max} and $AUC_{0\text{-}28d}$ at the highest SC dose (10 mg/kg) evaluated in the GLP toxicology study were approximately a factor 3.6 to 3.7 and 4.6 to 4.7 higher than the geometric mean C_{max} and $AUC_{0\text{-}inf}$ observed in patients after the first full dose of 60 mg (Cycle 1 Day 22), the highest dose evaluated in clinical studies.

The FDA's Assessment:

Epcoritamab TK parameters from the 5-week toxicology study in cynomolgus monkeys are described in Table 7; this study evaluated both the IV and SC routes of administration, whereas the clinical route of administration is SC only. Among animals administered repeated IV doses of epcoritamab, all animals at the ≤0.1 mg/kg dose levels and select males at the 1 mg/kg dose level tested positive for ADAs from Day 15 onwards (see Table 8). Epcoritamab concentrations in ADA-positive animals were low or non-quantifiable, and these animals were excluded from the TK evaluation.

Following a single IV dose of epcoritamab, 8/12 animals (~67%) were ADA-positive from Day 15 onwards, and following a single SC dose of epcoritamab 11/18 animals (~61%) were ADA-positive from Days 15 or 22 onwards (data not shown). Given these animals only received a single dose of epcoritamab, they were not excluded from the TK evaluation.

TK data from general toxicology studies:

A 5-Week Toxicity Study of GEN3013 by Intravenous Infusion and Subcutaneous Injection in Cynomolgus Monkeys with Bioavailability, Local Tolerance, and a 6 Week Recovery Period / (b) (4) 503484

Table 7: 5-Week Toxicology Study in Cynomolgus Monkeys, Summary of Mean Epcoritamab TK Parameters

Route	Day	Dose level (mg/kg)	Parameter					
			C_{max} (ng/mL)		AUC_{0-t} (ng·h/mL) #		AUC_{0-168h} (ng·h/mL) ^	
			Male	Female	Male	Female	Male	Female
IV infusion (repeat-dose)	1	0.01	102	95.7	161	143	164	146
		0.1	1,610	1,770	5,620	7,170	5,620	7,170
		1	24,000	24,600	573,000	649,000	573,000	649,000
	15	0.01*	-	-	-	-	-	-
		0.1*	-	-	-	-	-	-
		1	23,600 (n=4)	27,000	1,060,000 (n=4)	1,180,000	1,060,000 (n=4)	1,180,000
	29	0.01*	-	-	-	-	-	-
		0.1*	-	-	-	-	-	-
		1	37,200 (n=2)	28,500	2,400,000 (n=2)	1,980,000	2,020,000 (n=2)	1,710,000
IV infusion (single-dose)	1	0.1	1,610	1,300	13,200	4,250	-	-
		1	21,600	28,400	613,000	635,000	-	-
SC injection (single-dose)	1	0.1	244	111	37,000	16,100	-	-
		1	2,100	1,670	518,000	411,000	-	-
		10	35,900	35,100	9,330,000	9,230,000	-	-

0-t is from time zero to the time of the last observed quantifiable concentration; ^ 0-168h is the dosing interval (168 hours); * TK parameters were not reported at these dose levels as all animals exhibited a positive ADA response.

Table 8: 5-Week Toxicology Study in Cynomolgus Monkeys, Summary of Animals Positive for ADAs (Following Repeated IV Doses Only)

Dose level (mg/kg)	Sex	Pre-treatment	Day 15	Day 22	Day 29	Day 72
0.01	Male	0/3	3/3	3/3	3/3	N/A
	Female	0/3	3/3	3/3	3/3	N/A
0.1	Male	0/3	3/3	3/3	3/3	N/A
	Female	0/3	3/3	3/3	3/3	N/A
1	Male	0/3	1/5	3/5	3/5	1/2
	Female	0/3	0/5	0/5	0/5	0/2

N/A: not applicable (no recovery samples collected)

5.5.Toxicology

5.5.1. General Toxicology

The nonclinical toxicity profile of epcoritamab was established in a series of nonclinical safety studies in cynomolgus monkeys, the only cross-reactive toxicology species.
The primary toxicity findings in cynomolgus monkeys administered epcoritamab included adverse clinical signs (incidents of vomiting, decreased activity, hunched posture; and mortality [≥1 mg/kg IV]). These findings were considered associated with elevated cytokine levels, primarily following the first dose. SC administration of epcoritamab to cynomolgus monkeys was associated with lower C_{max} values and lower peak cytokine levels, but comparable B-cell depletion relative to the same IV dose (mg/kg). Other epcoritamab-related toxicity findings included reversible hematologic changes (alterations in leukocytes and lymphocytes), and reversible B-cell depletion in peripheral blood consistent with reversible decreases in lymphoid cellularity in lymphoid tissues observed microscopically. Overall, these toxicity findings are consistent with the pharmacologic activity of epcoritamab.
A 3-month repeat-dose toxicity study of epcoritamab in cynomolgus monkeys was waived for phase 3 trials and registration of epcoritamab across the ICH regions (FDA, EMEA, and PMDA) based on the inability to maintain sufficient exposures to epcoritamab with repeated dosing.

Study: A 5-Week Toxicity Study of GEN3013 by Intravenous Infusion and Subcutaneous Injection in Cynomolgus Monkeys with Bioavailability, Local Tolerance, and a 6 Week Recovery Period / (b) (4) 503484 / eCTD location 4.2.3.2

Key Drug-related Adverse Findings

- One female at 1 mg/kg IV sacrificed on Day 2 (12.75 hrs post dose) with adverse clinical signs (decreased activity, hunched posture, subdued, weak). The cause of the animal's demise was not determined histopathologically but was considered associated with elevated cytokines after the first dose.
- Clinical signs after IV and SC administration included incidents of vomiting, decreased activity, hunched posture, generalized reddened skin, and/or slightly uncoordinated movements primarily following the first dose at ≥ 0.1 mg/kg.
- Cytokine release following dose occasions (more pronounced following the first dose).
- Reversible B-cell depletion in peripheral blood consistent with decreases in lymphoid follicular cellularity in the spleen, lymph nodes and GALT noted by histopathology at ≥0.1 mg/kg.
- Following a 6-week recovery, decreased lymphoid cellularity remained present at slightly lower severity.
- There were no epcoritamab-related histopathological changes at the sites of IV or SC administration.

GLP compliance: Yes

Methods	
Dose and frequency of dosing:	**Groups 1 to 4:** 0, 0.01, 0.1, 1 mg/kg weekly (Q1Wx5) IV infusion **Groups 5 and 6:** 0.1, 1 mg/kg single IV infusion **Groups 7 to 9:** 0.1, 1.0, 10 mg/kg monthly SC injection (Days 1 and 29)
Route of administration:	IV: Groups 1 to 6 SC: Groups 7 to 9
Formulation/Vehicle:	IV: 0.9% saline; SC: 30 mM acetate buffer at pH 5.5 with 150 mM sorbitol
Species/Strain:	cynomolgus monkey / Macaca fascicularis (Mauritius)
Number/Sex/Group:	**Main toxicity:** 3M and 3F Groups 1 to 9. Termination Day 36 **Recovery:** 2M/2F; Groups 1 (0 mg/kg) and 4 (1 mg/kg IV). Termination Day 72
Age:	4-6 years
Satellite groups:	NA

Observations and Results

Noteworthy Findings	
Mortality	1 female (6501F at 1 mg/kg IV) was killed prematurely on Day 2 (12.75 hours post dose) due to adverse clinical signs (decreased activity, hunched posture, subdued and weak). The cause of the animal's demise was not determined histopathologically but was considered associated with elevated cytokines after the first dose.
Clinical Observations	After a single IV dose, decreased activity and hunched posture was observed between 4 and 6 hours postdose in males and females at 0.1 or 1 mg/kg; these findings were present at 12 hours postdose in females at 0.1 or 1 mg/kg. Isolated incidents of white foamy or yellow liquid vomit were noted within 2 hours postdose in males (0.1 or 1 mg/kg)and in females (1 mg/kg). Animals were considered normal 24 hours after a single dose. After repeat IV dosing, hunched posture was observed between 1 and 2 hours postdose on Day 8 in one male (4005M) at 1 mg/kg. There were no other drug-related clinical signs on Day 8 or other dosing days. After a single SC dose, decreased activity and hunched posture noted between 4 and 6 hours postdose in males and females at all dose levels; and still present at 12 hours postdose. Incidents of white, clear, or foamy vomit were noted at 4 hours postdose in males (all doses) and females (1 or 10 mg/kg). Isolated incidents of generalized reddened skin on the body surface noted between 4 and 12 hours postdose in males (all doses) and females (0.1 or 1 mg/kg). Slightly uncoordinated movements noted at 6 or 12 hours postdose in males (0.1 or 10 mg/kg) and females (1 or 10 mg/kg). No similar signs were observed after the Day 29 SC dose.
Body Weight (%)	No epcoritamab-related changes
Ophthalmology	No epcoritamab-related findings
Electrocardiology	No epcoritamab-related findings

Hematology	In general, following single or weekly IV dosing, Total leukocyte, lymphocyte, monocyte, basophil, and eosinophil counts were higher in males (0.1 or 1 mg/kg) and females (0.1 or 1 mg/kg) at various times during the dosing phase when compared with controls and pretreatment values. Counts were considered similar to control or pretreatment values by Day 29 or during the recovery period. Hemoglobin concentrations and hematocrits were slightly lower in males at 0.1 or 1 mg/kg during the dosing phase compared with controls and pretreatment values. In general, following single SC dosing, Total leukocyte, eosinophil, and monocyte counts were higher in most treated males and females at various times during the dosing phase when compared with pretreatment values. Counts were similar to pretreatment values on Days 29 and 33. Hemoglobin concentrations and hematocrits were slightly lower on Days 8, 15 and 22 in all treated male and female groups compared with pretreatment values.
Clinical Chemistry	No epcoritamab-related changes
Urinalysis	No epcoritamab-related changes
Organ weights	No epcoritamab-related changes
Gross pathology	No epcoritamab-related findings
Histopathology	Decreased lymphoid cellularity was observed in spleen, lymph nodes and GALT at 1.0 mg/kg IV (Groups 4 and 6), and at ≥ 1.0 mg/kg SC (Groups 8 and 9). The same finding was observed to a lesser extent at 0.1 mg/kg in single IV or SC dose males (Groups 5 and 7), and in females given 5 weekly IV doses or a single SC dose (Groups 3 and 7). Increased lymphoid cellularity was observed in spleen and mandibular lymph node in males given 5 weekly IV doses at 0.01 and 0.1 mg/kg (Groups 2 and 3). Decreased lymphoid cellularity was still present following a recovery period, with a slightly lower severity. Both routes of administration were well tolerated.
Anti-drug Antibodies	All animals dosed weekly IV at 0.01 or 0.1 mg/kg on Days 15 and 29 exhibited a positive ADA response, no TK parameters reported.
Cytokines	Increases in cytokine levels were highest after the first dose, and markedly less pronounced with subsequent doses. For most analytes, the highest initial response was observed in animals at 1 mg/kg IV (Group 6) and 10 mg/kg SC (Group 9). Peak levels for most cytokines at a comparable dose were generally lower following SC relative to IV administration.
Immunophenotyping *(findings from peripheral blood presented; lymph node and bone marrow results not summarized here)*	Decreases in all T cell populations immediately after dosing in males (all doses). Recovery to baseline values from Day 4 in majority of T cell populations. Single dose IV and SC animals recovered completely by Day 15. Decreases in Total B-cells immediately after dosing in all epcoritamab-treated groups. Males at 0.01 or 0.1 mg/kg recovered by Day 22; no sign of recovery even during the recovery period in males at 1 mg/kg. Females at 0.01 mg/kg started to show signs of recovery on Day 22, however, they did not fully recover. No sign of recovery after the first dose was observed in females at 0.1 or 1 mg/kg. Single dose IV or SC groups showed no signs of recovery after dosing in the Total B-cell population. Decreases in mature B-cells in all drug-treated male and female groups with no signs of recovery during the study period.

	Decreases in Naïve B-cells and Memory B cells in all epcoritamab-treated groups. Recovery at 0.01 or 0.1 mg/kg on Days 22 to 29. Single dose IV animals at 0.1 mg/kg showed similar signs of recovery on Day 22 but to a much lesser extent. All other dosing groups showed no signs of recovery.

General toxicology; additional studies

The main findings in the pivotal GLP toxicity study are consistent with the toxicities observed in the non-GLP single dose exploratory ((b) (4) 529668) and dose range-finding (b) (4) 501775) studies in cynomolgus monkeys administered epcoritamab.

The FDA's Assessment:

We agree that the cynomolgus monkey is a pharmacologically relevant nonclinical species to assess the toxicity of epcoritamab, and general toxicology studies in other species are not warranted. We also agree that longer-duration repeat-dose toxicity studies in cynomolgus monkeys would not provide meaningful information and are not warranted.

The purpose of the GLP-compliant 5-week repeat-dose toxicity study in cynomolgus monkeys was to determine the toxicity and TK of epcoritamab, including the relative bioavailability by the SC route. We agree with the Applicant's assessment of the results of the study as described above, and have the following additional comments:

- Dose-dependent increases in the plasma cytokines IL-2, IL-6, IL-8, IL-10, IL-15, IFN-γ, TNF-α, and MCP-1 were observed in all epcoritamab-treated groups after the first dose. Levels of plasma cytokines after the first dose generally correlated with epcoritamab plasma concentrations. Increases in IL-1β, IL-4, IL-12p40, IL-15, and TNF-α were also observed after the third dose in the 0.1 mg/kg IV group only; the reason(s) for the difference in group cytokine responses are unknown.
- Among animals administered repeated IV doses of epcoritamab, all animals at ≤0.1 mg/kg exhibited a positive ADA response, while only 3/5 males and 0/5 females at 1 mg/kg exhibited a positive ADA response. After repeated IV doses of epcoritamab, systemic exposure was only maintained at 1 mg/kg. Modest accumulation (as measured by $AUC_{0\text{-}168hr}$) was observed at 1 mg/kg on Day 15 (Day 15/Day 1 ratio of 1.8 for both sexes) and on Day 29 (Day 29/Day 1 ratio of 3.5 for males and 2.6 for females).
- Immunophenotyping was performed for peripheral blood samples, as well as lymph node and bone marrow biopsies. In the peripheral blood, the immediate decrease in T-cell populations followed by a rapid recovery may be the result of the transient redistribution of T-cells into other tissues. Immediate decreases in B-cells were observed in peripheral blood samples, as well as in lymph node and bone marrow biopsies at necropsy. Some B-cell populations in the peripheral blood at ≤0.1 mg/kg partially recovered by Day 29, and increases in precursor B-cells and immature B-cells were observed in the bone marrow of some epcoritamab-treated animals at the

recovery necropsy.

- Decreased cellularity in the lymphoid organs is consistent with the epcoritamab MOA, i.e., the depletion of CD20-positive cells. Increased lymphoid cellularity in the spleen and mandibular lymph node was observed in select males at 0.01 mg/kg and 0.1 mg/kg, and may represent an immunogenic response.
- Relative bioavailability could only be determined at 1 mg/kg; based on $AUC_{0\text{-}inf}$ (data not shown), epcoritamab bioavailability by the SC route was 85% in males and 49% in females.

5.5.2. Genetic Toxicology

The Applicant's Position:
Genotoxicity studies were not conducted for epcoritamab per ICHS6(R1) and ICH S9 guidance.

The FDA's Assessment:
We agree that genotoxicity studies are not needed to support the approval of BLA 761324.

5.5.3. Carcinogenicity

The Applicant's Position:
Carcinogenicity studies were not conducted for epcoritamab per ICHS6(R1), ICH S1A, and ICH S9 guidance.

The FDA's Assessment:
We agree that carcinogenicity studies are not needed to support the approval of BLA 761324.

5.5.4. Reproductive and Developmental Toxicology

Per ICH S9, studies of fertility and early embryonic development, and pre- and postnatal toxicity were not conducted. In the GLP toxicity study ((b) (4) 503484), there were no epcoritamab-related macroscopic or microscopic pathologic findings in the reproductive organs of 4 to 6 year-old male or female cynomolgus monkeys. An EFD toxicity study of epcoritamab in cynomolgus monkeys was waived for phase 3 trials and registration of epcoritamab across ICH regions (FDA, EMEA, and PMDA) given the high potential for immunogenicity of epcoritamab in cynomolgus monkeys. A risk assessment-based on a weight of evidence approach was conducted considering the mechanism of action of epcoritamab and relevant information from other B-cell targeting agents (Module 2.6.6). Epcoritamab has the potential to be transmitted from the pregnant mother to the developing fetus, and based on its mechanism of action, fetal exposure to epcoritamab may cause adverse, but reversible, developmental outcomes, including B-cell lymphocytopenia and alterations in normal immune responses in infants exposed in utero.

The FDA's Assessment:

We agree with the Applicant's WOE-based approach for the assessment of reproductive and developmental toxicity.

Epcoritamab is a T-cell redirecting bsAb and causes the T-cell dependent depletion of CD20-positive cells. Risks associated with T-cell activation include cytokine release and associated inflammatory effects. CD20 is expressed on the surface of normal B-cells, and epcoritamab caused B-cell depletion in the 5-week toxicity study in cynomolgus monkeys. The occurrence of inflammatory AEs in the mother may adversely affect the pregnancy. Epcoritamab binds the FcRn and may cross the placenta to the developing fetus similarly as an endogenous IgG antibody. In utero exposure to epcoritamab is expected to affect immune system function in the developing fetus and neonate. Epcoritamab is an IgG1-based bsAb and may be present in milk; a breastfed child may be exposed to epcoritamab via lactational transfer.

The approval of BLA 761324 does not rely on product-specific published literature.

5.5.5. Other Toxicology Studies

The Applicant's Position:
Key findings are summarized in the following for in vitro studies of species cross-reactivity, cytokine release, hemolytic potential, and tissue cross-reactivity.

Study: Evaluation of species cross-reactivity of DuoBody-CD3xCD20 in vitro / GMB3013-034 / eCTD location 4.2.3.7.7
Species cross-reactivity was evaluated using flow cytometry and CD20-expressing cells from human, cynomolgus monkey, dog, rabbit, pig, rat, or mouse, as well as X-ray crystallographic structural characterization of the Fab fragment of IgG1 CD3 FEAL (the parental antibody for the CD3-specific Fab-arm in epcoritamab).
Key Findings: Epcoritamab bound to both human and cynomolgus monkey CD3. Epcoritamab also bound to human and cynomolgus monkey CD20-expressing human embryonic kidney (HEK) cells with a comparable EC50 value (~0.4 µg/mL), and to rabbit CD20 with a higher EC50 (1.04 µg/mL), but not to CD20 of the other species evaluated (dog, rabbit, pig, rat, or mouse).
GLP compliance: No

Study: ProStorm® Cytokine Release Assay / 32318 / eCTD location 4.2.3.7.7
Cytokine release was evaluated in vitro using a soluble human whole blood format. A soluble assay format was selected to avoid CD3 crosslinking possible with immobilized antibody formats.
Key Findings: Epcoritamab at ≥1600 pg/mL was associated with concentration-related cytokine release (IL-2, IL-6, IL-8, IL-10, IFNγ, and TNFα). No concentration-dependent response was noted for IL-4 and no cytokine levels were detected at epcoritamab concentrations ≤320 pg/mL.
GLP compliance: No

Study: Evaluation of the Hemolytic Potential of GEN3013 in Human Whole Blood in vitro and Plasma Compatibility Assessment / (b) (4) 301352 / eCTD location 4.2.3.7.7
In vitro assay using human whole blood evaluating epcoritamab for potential hemolysis of human blood in vitro along with plasma compatibility evaluation.
Key Findings: Epcoritamab (at 1 or 20 µg/mL) was non hemolytic and showed no signs of clumping of red cells in whole blood; and no precipitation in plasma.
GLP compliance: Yes

Study: Assessment of the Potential Cross Reactivity of GEN3013 with a Selected Panel of Human and Cynomolgus Monkey Tissues / (b) (4) 8361457 / eCTD location 4.2.3.7.7
In vitro tissue cross reactivity study using cryo-sections from control and a panel of human and cynomolgus monkey tissues (40 separate tissues; three donors for each tissue). Three concentrations of FITC-labelled epcoritamab were evaluated: 0.625, 1.25, and 2.5 µg/mL.
Key Findings: Binding of epcoritamab was comparable across species and limited to mononuclear cells in various tissues. As CD3 and CD20 are expressed on T and B cells, respectively, the staining of blood lymphocyte and tissue mononuclear cells was expected reactivity.
GLP compliance: Yes

The FDA's Assessment:
We agree with the Applicant's assessment of the GLP-compliant tissue cross-reactivity study and the hemolytic potential study. No unanticipated cross-reactivity was observed in the tissue cross-reactivity study. The FDA's Assessment of the in vitro species cross-reactivity information is described in Section 5.3 Pharmacology.

We also agree with the Applicant's assessment of the non-GLP-compliant cytokine release assay. In the cytokine release assay, the average EC_{50} value for each cytokine (excluding IL-4) was 11.6 ng/mL to 43.1 ng/mL.

The epcoritamab container closure system was evaluated in an extractables study under defined extraction conditions and in a leachables study with the epcoritamab drug product. Extractables studies were also conducted on product contact materials used in the drug product manufacturing process. The Applicant submitted toxicological risk assessments which concluded that the levels of the compounds identified posed a negligible risk to patients; we agree with the conclusions of the toxicological risk assessments.

X	X
Michael Manning, PhD Primary Reviewer	Brenda Gehrke, PhD Supervisor

6 Clinical Pharmacology

6.1.Executive Summary

The FDA's Assessment:

Epcoritamab is a T-cell engaging bispecific antibody that binds to the CD3 expressed on the surface of T-cells and CD20 expressed on the surface of lymphoma cells and healthy B-lineage cells. The Applicant is seeking approval of epcoritamab for the treatment of patients with relapsed or refractory (R/R) large B-cell lymphoma (LBCL) who have received at least two prior systemic therapies. The proposed subcutaneous (SC) dosing regimen is shown in Table 9 below (hereafter referred to as 0.16/0.8/48 mg). The proposed dosage is administered until disease progression or unacceptable toxicity.

Table 9: Recommended Dose and Schedule (28-Day Treatment Cycles)

Dosage schedule	Cycle of treatment	Days	Dose
Weekly	Cycle 1	1	0.16 mg (Step-up dose 1)
		8	0.8 mg (Step-up dose 2)
		15	48 mg (Full dose)
		22	48 mg
	Cycles 2 and 3	1, 8, 15 and 22	48 mg
Every two weeks	Cycles 4 to 9	1 and 15	48 mg
Every four weeks	Cycle 10 and beyond	1	48 mg

The primary efficacy and safety evidence supporting the proposed dosage regimen results from the pivotal LBCL expansion cohort in Study GCT3013-01, an ongoing first-in-human, multicenter, open-label, Phase I/II dose escalation and expansion study, which demonstrated an objective response rate (ORR) of 63% and a complete response rate (CR) of 39%, as well as an overall acceptable safety profile.

The key review issues are focused on the evaluation of dose selection, recommendations for restarting therapy after dose delay, drug-drug interaction (DDI) due to cytokine release, and immunogenicity.

Recommendations

The Office of Clinical Pharmacology has reviewed the information submitted in BLA 761324. This BLA is approvable from a clinical pharmacology perspective. The key review issues with specific recommendations/comments are summarized below in Table 10.

Table 10: Key Clinical Pharmacology Review Issues and Recommendations by FDA

Review Issue	Recommendations and Comments
Pivotal and supportive evidence of effectiveness	The primary evidence of effectiveness comes from the pivotal LBCL RP2D cohort in study GCT3013-01. The proposed dosage regimen (0.16/0.8/48 mg) is supported by an ORR of 63% and CR of 39% in patients with R/R LBCL.
General dosing instructions	The proposed dosage regimen (0.16/0.8/48 mg) is selected with the following rationale: • The step-up doses (0.16/0.8/48 mg) are clinically active doses that help mitigate the risk of CRS in the subsequent full therapeutic doses at 48 mg. • CRS grade and incidence for each dose event did not differ significantly across body weight quartiles. • Exposure-response (E-R) safety analysis did not identify any safety concerns with exposure following the proposed dosage of 0.16/0.8/48 mg. • E-R efficacy analyses identified positive associations between Cycle 1 AUC and ORR, CR rate, OS, and PFS which support the proposed dosage of 0.16/0.8/48 mg. The treatment duration is supported by observed efficacy data showing that: • Majority (94%) of initial responses (CR or partial response (PR)) were achieved during the initial once weekly (QW) dosing window (median time to initial response ~1.4 months). · Majority of LBCL responders who were treated during the 48 mg every 2 weeks (Q2W) and 48 mg every 4 weeks (Q4W) dosing windows maintained or improved response during Q2W and Q4W dosing windows compared to the preceding dosing windows.
Dosage recommendations for restarting therapy after dose delay	The proposed dosage recommendation for restarting therapy after dose delay aims to mitigate CRS risk and is supported by: • No increase in the risk of CRS following dose delays shorter than the proposed cut-offs for re-priming when compared to the overall RP2D expansion cohort. • Population pharmacokinetic (popPK) simulations predicted that epcoritamab concentration remained above the trough concentrations prior to the last step-up dose following dose delays shorter than the proposed cut-offs for re-priming.

Review Issue	Recommendations and Comments
Dosing in patient subgroups (intrinsic and extrinsic factors)	No dosage adjustment is needed according to weight, age, sex, White and Asian racial category, mild to moderate renal impairment, or mild hepatic impairment.
Drug-drug interactions	Epcoritamab administration resulted in transient release of cytokines, which may suppress CYP450 enzymes and cause drug-drug interactions. Increased exposure of CYP450 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 on Cycle 1 Day 15 and during and after CRS. Monitor for toxicity or concentrations of drugs that are CYP450 substrates where minimal concentration changes may lead to serious adverse reactions. Adjust the dose of the concomitant drug as needed.
Immunogenicity	Anti-epcoritamab antibodies developed in 2.6% of patients during epcoritamab treatment at 0.16/0.8/48 mg RP2D dosage in the LBCL cohort in Study GCT3013-01.
Labeling	Overall, the proposed labeling recommendations are acceptable upon the Applicant's agreement with the FDA -recommended revisions to the labeling.

Postmarketing Requirements and Commitments

The Applicant is requested to conduct the following clinical pharmacology studies as a postmarketing requirement (PMR) or postmarketing commitment (PMC). The PMR/PMC studies will be included in the Approval letter with milestones agreed upon after negotiation with the Applicant.

PMC or PMR	Key Issue(s) to be Addressed	Rationale	Key Considerations for Design Features
☐ PMC ☒ PMR	Determination of epcoritamab dose and assessment of PK and safety in pediatric patients with mature B-cell lymphoma.	No study of epcoritamab was performed in the pediatric population.	Conduct of a clinical trial to confirm the appropriate dose of epcoritamab and to assess the safety, PK, and preliminary efficacy of epcoritamab monotherapy in pediatric patients with relapsed or refractory aggressive mature B-cell lymphoma.

PMC or PMR	Key Issue(s) to be Addressed	Rationale	Key Considerations for Design Features
☒ PMC ☐ PMR	Characterization of PK and pharmacodynamics (PD), in addition to safety and efficacy, in a population representative of the US patient population with LBCL.	No PK data to assess the impact of racial categories other than White or Asian in the reported clinical trials	Conduct an integrated analysis of data from clinical trials to further characterize the safety, efficacy, PK, and PD of epcoritamab monotherapy among U.S. racial and ethnic minority patients with large B-cell lymphoma. The population should be representative of the U.S. population, including racial and ethnic diversity, of patients with LBCL and allow for interpretation of the results in these population.

6.2.Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Data:

Pharmacokinetics:

Absorption

The PK profile of epcoritamab SC was characterized by slow absorption. Following administration of the proposed full dose of 48 mg, the t_{max} was approximately 3 to 4 days.

Distribution

The geometric mean (CV%) central volume of distribution is 8.27 L (27.5%) in LBCL patients based on popPK modeling. Protein-binding studies using human serum albumin are not applicable to therapeutic biologics and were not conducted.

Metabolism

No metabolism studies in humans have been conducted with epcoritamab. As an IgG antibody, epcoritamab is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG.

Elimination

Total clearance decreased with increasing epcoritamab concentration over time. Target-mediated elimination (approximated by QSS in the PopPK model) was responsible for most epcoritamab elimination following administration of the 0.16 mg priming dose (C1D1) and 0.8 mg intermediate doses (C1D8). After the first full dose of 48 mg epcoritamab (C1D15), mean total clearance decreased rapidly and approached the linear clearance, suggesting saturation of target-mediated clearance. In addition, the total clearance was similar between subjects

administered 48 mg and 60 mg full doses, but slower than those administered 24 mg or lower doses, indicating approximately linear PK of epcoritamab and a plateau of tumor killing has been achieved for doses equal or exceeding 48 mg.
The geometric mean (CV%) clearance is 0.441 L/day (27.8%) following the full dose of 48 mg in subjects with LBCL in the GCT3013-01 trial. The half-life of epcoritamab is concentration dependent. The model-derived geometric mean half-life values according to washout period ranged approximately 22 to 25 days for the full dose of 48 mg based on frequency of dosing (QW, Q2W, or Q4W).

Immunogenicity:

A total of 4 (2.5%) of 158 ADA-evaluable subjects with LBCL in the GCT3013 01 trial (ESC+EXP) who received epcoritamab at the proposed dosing regimen were ADA positive on treatment (but not at baseline), all with low titers. Among these 4 subjects, 1 subject was transiently ADA-positive at C1D22, C3D1, C3D22, and C4D1 and confirmed ADA-negative for all other time points; 1 subject was transiently ADA-positive from C2D22 to C4D1 and confirmed ADA-negative for all other time points; 1 subject was ADA-positive from C1D22 through the end of treatment at C2D16; and 1 subject was ADA-positive from C2D1 through the end of treatment at C2D8.
In the popPK analysis, no meaningful differences in PK were detected between ADA-negative and ADA-positive subjects after adjusting for other covariates.
Due to the low number of subjects with ADAs, a definitive analysis of the impact of ADAs on efficacy and safety could not be conducted. Of the 4 LBCL subjects who were ADA-positive on treatment and not at baseline, 2 subjects discontinued epcoritamab treatment within the first 2 cycles due to PD, and the other 2 subjects had a BOR of CR as assessed by IRC with DORs of 9.69 and 15+ months. No notable safety issues were observed in the 4 ADA-positive subjects. These data, although limited (n=4) showed no evidence of ADA impact on safety and tolerability in these subjects.
Overall, the low number of subjects with ADAs observed suggests a low risk for immunogenicity with epcoritamab using the proposed dosing regimen.

Pharmacodynamics:

The proposed mechanism of action of epcoritamab is induction of T-cell-mediated cytotoxicity of CD20-expressing cells with associated T-cell activation and proliferation, upon simultaneous binding to CD20 on lymphoma cells and CD3 on T cells.
In subjects who had detectable peripheral B cells at treatment initiation, epcoritamab induced depletion of circulating B cells (defined as CD19 B-cell counts <10 cells/µl in subjects who have detectable B cells at treatment initiation) after the first full dose (48 mg), which was sustained while subjects remained on treatment.
A transient decrease in circulating T cells was observed within 6 to 14 hours after the initial priming dosing of epcoritamab (0.16 mg on C1D1). The level of T cells rapidly returned to baseline, consistent with T cell margination that has been reported for other CD3 T cell-redirecting antibodies (Nagele et al., 2017). Subsequent treatment with epcoritamab induced

expansion and activation of circulating T cells from baseline, consistent with the proposed mechanism of action.
Following SC administration of epcoritamab, transient and modest elevations of circulating levels of selected cytokines (IFN-γ, TNFα, IL-6, IL-2, and IL-10) occurred, mostly after the first full dose (48 mg; C1D15) with peak levels between 1 and 4 days postdose. Levels returned to baseline prior to administration of the second full dose (C1D22).

The Applicant's Position:
The PK, pharmacodynamic, and pharmacometric assessments presented provide a thorough description of epcoritamab disposition and pharmacodynamics for subjects with R/R LBCL after 2 or more lines of systemic therapy

The FDA's Assessment:
The epcoritamab clinical pharmacology program included data from dose escalation and LBCL cohort in the expansion phase of Study GCT3013-01 (Table 11).

Table 11: Dose Escalation in patients with R/R B-Cell NHL (N= 68) and Dose Expansion in patients with R/R LBCL (N=157) of epcoritamab SC monotherapy in Study GCT3013-01

Escalation Cohort*	N	Dose Level (mg)				
		QW		Q2W	Q4W	
		C1D1	C1D8	C1D15-C2	C3-6: D1 & 15	C≥7D1
1	1	0.004	0.0128	0.0128	0.0128	0.0128
2	2	0.0128	0.04	0.04	0.04	0.04
3	4	0.04	0.12	0.12	0.12	0.12
3a	1	0.04	0.38	0.38	0.38	0.38
4	1	0.12	0.38	0.38	0.38	0.38
5	7	0.04	0.76	0.76	0.76	0.76
6	5	0.04	0.25	1.5	1.5	1.5
7	6	0.04	0.5	3	3	3
8	7	0.04	0.5	6	6	6
8a	2	0.08				
9	3	0.4	0.8	12	12	12
9a	4	0.08	1.6			
10	6	0.04	0.8	24	24	24
10a	4	0.16				
11	3	0.08	0.8	48	48	48
11a	9	0.16	0.8			
12	3	0.16	0.8	60	60	60

Expansion Cohort		QW		Q2W	Q4W	
		C1D1	C1D8	C1D15-C3	C4-9	C≥10
LBCL**	157	0.16	0.8	48	48	48

**RP2D regimen (0.16/0.8/48 mg) was selected based on the safety, efficacy, PK, and pharmacodynamic data from the Dose Escalation Part, in combination with population-PK modeling, PK/PD modeling, exposure-response analysis, and exposure-AE analysis
R/R = relapsed/refractory, NHL=non-Hodgkin lymphoma, SC=subcutaneous
*Source: Table 14.1.11, GCT3013-01 ESC, Module 5.3.5.2

The results from these groups and cohorts generally provide adequate characterization of epcoritamab pharmacokinetic properties.

Absorption: The drug product is administered subcutaneously. The median (range) T_{max} of epcoritamab after the first full dose and end of the weekly dosing regimen (end of Cycle 3) treatment doses were 4.0 (0.3 to 7) days and 2.3 (0.3 to 3.2) days, respectively.

Distribution: The geometric mean (CV%) apparent total volume of distribution of epcoritamab is 25.6 L (82%).

Elimination: The geometric mean (CV%) terminal half-life a full dose of epcoritamab (48 mg) ranged from 22 (58%) at the end of Cycle 3. The geometric mean (CV%) apparent total clearance is 0.53 L/day (40%) at the end of Cycle 3. Epcoritamab is expected to be metabolized into small peptides by catabolic pathways.

Dose proportionality: Epcoritamab area under the concentration-time curve (AUC) increased more than proportionally over a full dosage range from 1.5 to 60 mg.

Refer to Table 22 in Section 6.3.1 for details of PK and pharmacodynamics (PD) of epcoritamab.

6.2.2. General Dosing and Therapeutic Individualization

6.2.2.1. General Dosing

Data:
The proposed dosing regimen includes an initial priming dose of 0.16 mg (C1D1), an intermediate dose of 0.8 mg (C1D8), and a full dose of 48 mg at C1D15, C1D22, and thereafter. Epcoritamab is administered by SC injection in 28-day cycles, with QW dosing in Cycles 1 to 3, Q2W dosing in Cycles 4 to 9, and Q4W dosing in Cycle 10+ until unacceptable toxicity or disease progression.
The Dose Escalation Part of the GCT3013-01 trial evaluated a wide range of epcoritamab doses ranging from 0.004 mg up to 60 mg and dosing regimens (ie, a total of 17 cohorts) in subjects with R/R NHL, including priming doses ranging from 0.004 to 0.16 mg, intermediate doses ranging from 0.25 to 1.6 mg, and full doses ranging from 0.0128 to 60 mg. This step-up dosing

method was implemented to mitigate the incidence and severity of CRS, the most common epcoritamab-related TEAE.
The rationale for the selection of the proposed epcoritamab dosing regimen (including population PK modeling, exposure-efficacy, exposure-safety, and pharmacodynamic analyses) is summarized in Section 6.3.2.2.

The Applicant's Position:
The recommended dose and dosing schedule of epcoritamab in patients with R/R LBCL is supported by clinical data, population PK modeling, pharmacodynamic, and exposure-response analyses for efficacy and safety.

The FDA's Assessment:
FDA agrees that the proposed dosing regimen of epcoritamab is acceptable for the indicated patient population. The rationale for the dose selection is as follows:

- Step-up dosing regimen
  1) The step-up doses of 0.16 mg and 0.8 mg are clinically active doses. In patients with R/R B-cell lymphoma, the minimum efficacious dose was 0.12 mg, as shown in Table 12.

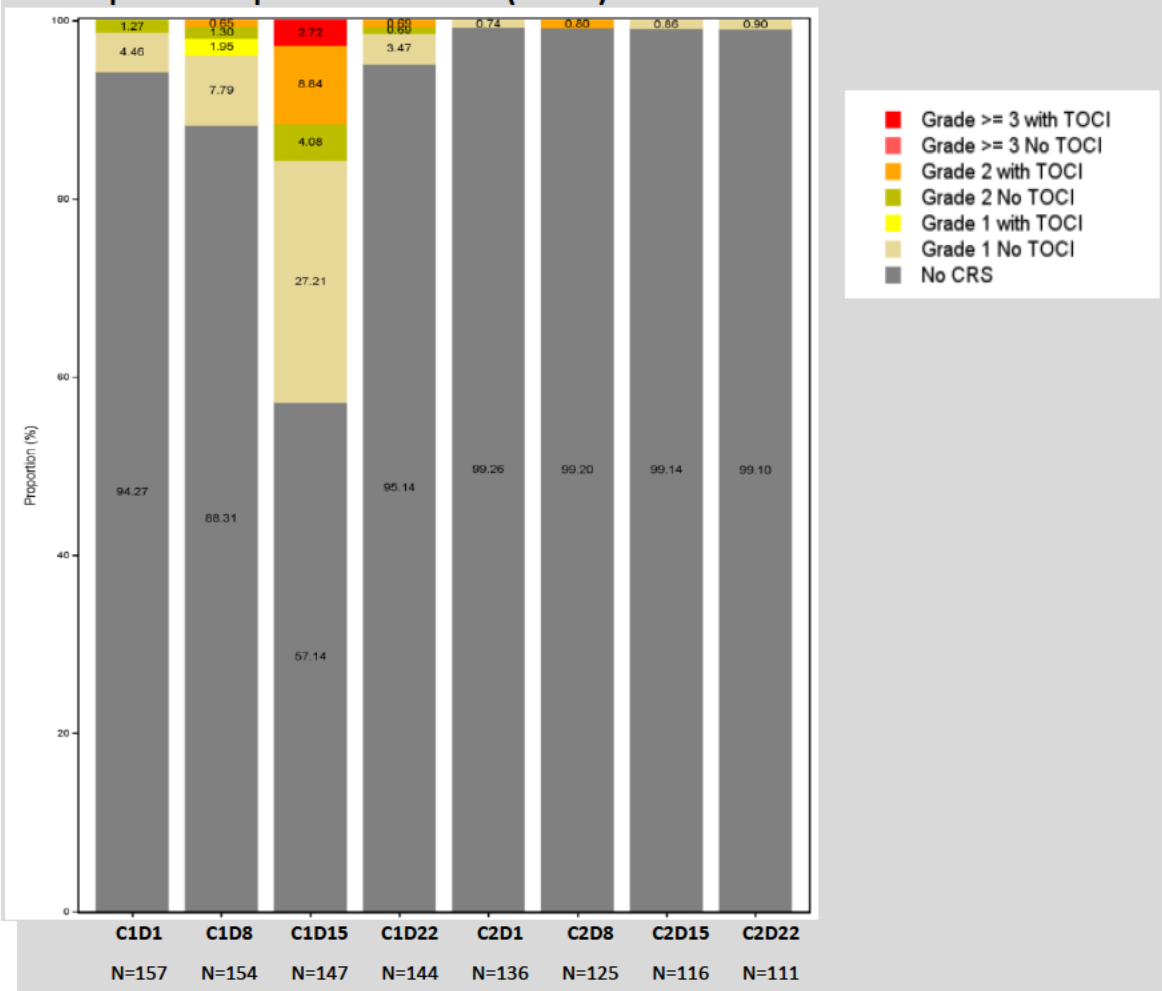
Table 12: Efficacy (by Lugano) by full dose cohort in patients with R/R B-Cell NHL

Cohort	Dose Level (mg)	Total (N)	CR*	ORR**
3	0.04/0.12	4	1 (25%)	1 (25%)
5	0.04/0.76	7	1 (14%)	2 (28%)
7	0.04/0.5/3	6	2 (33%)	3 (50%)
8	0.04/0.5/6	9	1 (11%)	3 (33%)
8a	0.08/0.5/6			
9	0.4/0.8/12	7	5 (71%)	5 (71%)
9a	0.08/1.6/12			
10	0.04/0.8/24	10	4 (40%)	5 (50%)
10a	0.16/0.8/24			
11	0.08/0.8/48	12	3 (25%)	8 (67%)
11a	0.16/0.8/48			
12	0.16/0.8/60	3	3 (100%)	3 (100%)

*CR=Complete Response, *ORR = CR+Partial Response (PR)
Source: Table 14.2.1, CSR, GCT3013-01 ESC, Module 5.3.5.2

  2) Cytokine release syndrome (CRS) mainly occurred following the first 3 doses in Cycle 1. The highest number of CRS events occurred after the first full dose (48 mg) on C1D15, and the risk of CRS in subsequent cycles was mitigated in patients with LBCL (LBCL cohort) receiving the proposed epcoritamab dosage of 0.16/0.8/48 mg. See Table 13 and Figure 1.

Figure 1: Summary of CRS events by dose event with 0.16/0.8/48 mg in Study GCT3013-01 Dose Expansion in patients with LBCL (n=157)



C1D1 = Cycle 1 Day 1; CRS=cytokine release syndrome, TOCI=tocilizumab
Source: Figure 1, Response to 22Nov2022 IR, SDN 8

Table 13: Summary of CRS events in Study GCT3013-01 ESC+EXP by dosing period in patients with LBCL who received 0.08/0.16/48 mg

	Dose Event					Overall
	Step-up Dose 1 (0.16 mg)	**Step-up Dose 2** (0.8 mg)	**First Full Dose** (48 mg)	**Second Full Dose** (48 mg)	**Third Full Dose and after** (48 mg)	**Any time**
	N=167	N=163	N=156	N=151	N=143	N=167
Patients with ≥1 CRS event	6.6%	12.9%	**43.6%**	4.6%	2.8%	50.3%
Grade 1	4.8%	10.4%	**26.9%**	3.3%	1.4%	31.1%
Grade 2	1.8%	2.5%	**14.1%**	1.3%	1.4%	16.8%
Grade 3	0	0	2.6%	0	0	2.4%

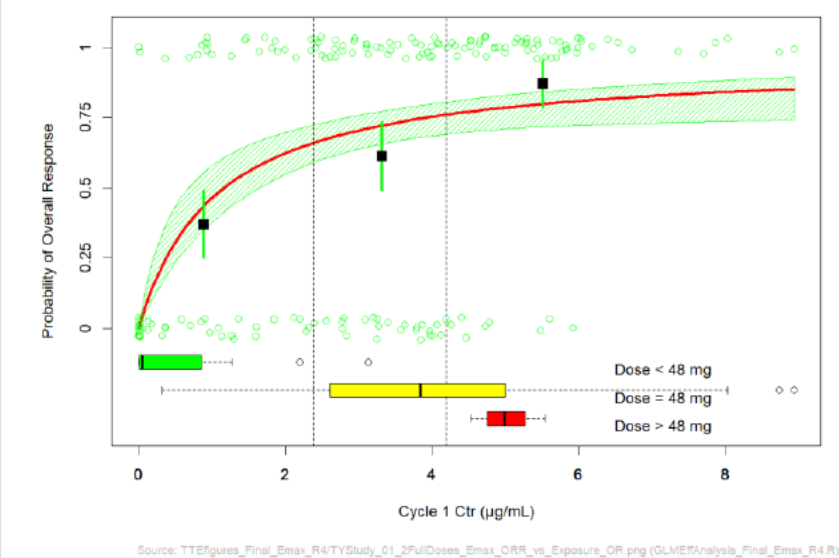
CRS=cytokine release syndrome
Source: Summary of Clinical Safety, Tables 18 and 19

3) Although lower body weight (<65 kg) was associated with 37% higher exposure compared to patients weighing 65 to 85 kg, the CRS grade and incidence for each dose event did not differ significantly across body weight quartiles in patients with LBCL (refer to Appendix 19.4.4.2 for details).

- **Full dose**

1) Modeling and simulations including E-R and PK/PD modeling analyses suggest higher epcoritamab exposure was associated with higher ORR and CR rates, with a potential plateau of efficacy following the proposed dosage regimen and above (Figure 2). Refer to Appendix 19.4.5.2 for detailed E-R efficacy analysis and for PK/PD analysis.
2) E-R safety analysis did not identify any safety concerns with the proposed dosage regimen. No E-R associations were observed for safety endpoints, including Grade ≥3 treatment emergent adverse events (TEAE), serious TEAE, Grade ≥3 infections, injection site reactions, TEAE leading to dose delay or dose discontinuations, any grade CRS, Grade ≥2 CRS, CRS requiring tocilizumab, immune effector cell-associated neurotoxicity syndrome (ICANS), and clinical tumor lysis syndrome (CTLS). Refer to Appendix 19.4.5.4 for detailed E-R safety analyses.

Figure 2: Emax model of overall response rate and epcoritamab Cycle 1 Ctrough in patients with LBCL in Study GCT3013-01



Source: TTEfigures_Final_Emax_R4/TYStudy_01_2FullDoses_Emax_ORR_vs_Exposure_OR.png (GLMEffAnalysis_Final_Emax_R4.R)

Green, yellow, and red boxplot summarizes Cycle 1 C_{trough} in patients with LBCL who received <48 mg full dose, 48 mg full dose, and >48 mg full dose, respectively. The red solid line and green shaded area represent the logistic regression model prediction and 95% CI of predictions. Points show exposure of individual patients with events (p=1) and without events (p=0). Black squares and vertical green lines show observed fraction of patients with events in each exposure group and 95% CI for these fractions. Dashed vertical lines show bounds of exposure tertiles. Data cutoff date: 31 Jan 2022.

CI = confidence interval; Ctr = C_{trough} (trough concentration); E_{max} = maximal effect; LBCL = large B-cell lymphoma.
Source: Figure 6 in Applicant's 2 December 2022 response to 22 November 2022 information request

- **Change in Dosing Intervals**
  1) The majority of initial responses (94%) were achieved in QW dosage window (i.e., within first 3 cycles), with a median time to response (defined as the time from C1D1 to first documentation of objective tumor response) of 1.4 months (range: 1, 8.4).
  2) The majority of LBCL responders treated during Q2W and Q4W dosage window maintained or improved response during Q2W or Q4W dosing (**Table 14**).

Table 14: Summary of ORR (IRC-Lugano) by dosage window in patients with LBCL in Study GCT3013-01

Dosage Window	Responders at the start of window (n)	Response (% Responders)		
		Maintained	Improved	Maintained or Improved
QW	93	76%	11%	87%
Q2W	81	52%	26%	78%
Q4W*	48	83%	4%	87%

*Majority of patients in Q4W window had 12 to 13 cycles. 30June2022 data cut-off.
LBCL = large B-cell lymphoma; ORR = overall response rate; QW = once weekly; Q2W = every 2 weeks; Q4W = every 4 weeks.
Source: Table fda.Ir2.q4.response2 , Response to 22Nov2022 IR Response, SDN 8

3) Longer Q4W administration appears to maintain response. Of the 18 responders with >18 cycles and response assessment at Cycle 18, 89% maintained response. Nonetheless, the available patient data is limited at Q4W with longer follow-up.

6.2.2.2. Therapeutic Individualization

Data:

The impact of intrinsic and extrinsic factors on epcoritamab exposures was evaluated using popPK modeling. The factors assessed included baseline body weight, sex, age, race, baseline renal impairment, baseline hepatic impairment, immunogenicity, geographic region, and baseline disease characteristics including prior therapies. No clinically relevant effect on exposure to epcoritamab was observed after accounting for differences in body weight. While body weight was the main covariate identified that had a significant effect on epcoritamab PK (the average AUC during Cycle 1 was 10.6% lower in subjects with weight ≥85 kg and 47.6% higher in subjects with weight <65 kg), no clinically meaningful differences in efficacy or safety in subgroups were observed.

The Applicant's Position:

No adjustment of epcoritamab dose is needed based upon the intrinsic or extrinsic factors examined. As a result, flat dosing of epcoritamab (ie, no adjustment for body weight) is proposed. No subjects with severe to end-stage renal disease (CrCl <30 mL/min) or severe hepatic impairment (total bilirubin >3 times ULN and any AST) have been studied. There is very limited data (n=1) in moderate hepatic impairment (total bilirubin >1.5-3 times ULN and any AST).

The FDA's Assessment:

The FDA agrees with the Applicant's position that no dose adjustment is needed according the investigated intrinsic and extrinsic factors. The Applicant's popPK analysis for epcoritamab is considered acceptable for the purpose of supporting the objectives (refer to Appendix 19.4.4 for details).

Associations between Cycle 1 AUC and intrinsic and extrinsic factors are displayed in Figure 9 of Section 6.3.2.3 with additional details in Appendix 19.4.4. None of the investigated patient factors were found to be associated with a clinically significant impact on exposure following the proposed dosage regimen.

In B-NHL patients with PK data who received the recommended dosage of epcoritamab (n=325), Cycle 1 median AUC was 13% lower in the higher body weight (BW) group (85 kg and above) and 37% higher in the lower BW group (less than 65 kg) compared to patients with BW of 65 to less than 85 kg. Body weight was not associated with any observed differences in CRS incidence or grade per dose event in GCT3013-01 patients with LBCL (n=157).

Mild (CLcr ≥60 mL/min to <90 mL/min) and moderate (CLcr ≥30 mL/min to <60 mL/min) renal impairment were associated with 34% and 36% higher AUC, respectively (Figure 9). Patients with mild and moderate renal impairment had 17% and 26% lower mean BW, respectively, compared to patients with normal renal function (CLcr ≥90 mL/min), and after accounting for the effect of body weight there were no significant differences in AUC across renal impairment subgroups.

Dosage adjustment is not recommended for body weight, age (20 to 89 years), sex, White or Asian racial category, mild to moderate renal impairment (CLcr ≥30mL/min to <90 mL/min), or mild hepatic impairment (total bilirubin ≤ ULN and AST > ULN, or total bilirubin 1 to 1.5 times ULN and any AST). The effects of severe renal impairment (CLcr <30 mL/min), end-stage renal disease, and moderate to severe hepatic impairment (total bilirubin > 1.5 times ULN and any AST) on the PK of epcoritamab are unknown.

PK data were available for 185 White patients (57%), 99 Asian patients (30%), 1 Native Hawaiian or Other Pacific Islander patient (0.3%), and 42 patients with race recorded as "missing, other, or not reported" (13%). As reported, there were no Black or African American

patients or Hispanic patients. Therefore, data were inadequate to assess the impact of racial categories other than White or Asian on PK. The FDA will issue a post marketing commitment (PMC) to characterize the safety, efficacy, PK, and PD of epcoritamab monotherapy among U.S. racial and ethnic minority patients with LBCL to adequately reflect the U.S. patient population and allow for interpretation of the results in these patient populations (see 6.2.2.4). The popPK analysis will be updated when more information becomes available to evaluate the PK differences among racial and ethnic subgroups.

6.2.2.3. Dosage Recommendations for Restarting Therapy after Dose Delay

The Applicant proposed the dosage recommendation as listed in Table 15 for restarting therapy after dose delay.

Table 15: Epcoritamab treatment recommendation for missed or delayed dose

Last Dose Administered	Time Since the Last Dose Administered	Action for Next Dose(s)[a]
0.16 mg on Cycle 1 Day 1		(b) (4)
	More than 8 days	Repeat 0.16 mg, then administer 0.8 mg the following week, followed by two weekly doses of 48 mg. Then resume the planned dosage schedule beginning with Day 1 of the subsequent cycle.
0.8 mg on Cycle 1 Day 8	14 days or less	Administer 48 mg then resume the recommended dosage schedule
	More than 14 days	Repeat 0.16 mg, then administer 0.8 mg the following week, followed by two weekly doses of 48 mg. Then resume the planned dosage schedule beginning with Day 1 of the subsequent cycle.
48 mg on Cycle 1 Day 15 onwards	6 weeks or less	Administer 48 mg, then resume the recommended dosage schedule
	More than 6 weeks	Repeat 0.16 mg, then administer 0.8 mg the following week, followed by two weekly doses of 48mg. Then resume the planned dosage schedule beginning with Day 1 of the subsequent cycle.
[a] Administer pretreatment medication prior to epcoritamab dose and monitor patients accordingly.		

(b) (4)

(b) (4). In GCT3013-01 expansion phase, only 3 patients received re-priming following dose delay. One patient received re-priming 13 days after step-up dose 1 (0.16 mg), one patient received re-priming >42 days after their last QW full dose, and one patient received re-priming >42 days

after their last Q2W full dose. None of these patients experienced CRS during the re-priming cycle.

The recommendations in Table 15 are supported by the following:

1) Dose delays without re-priming were observed for some patients in Study GCT3013-01. Evaluation of CRS events following dose delays without re-priming in the expansion phase of GCT3013-01 (Table 16) indicated no increase in the risk of CRS following dose delays that were less than the proposed cut-offs for re-priming when compared to overall RP2D expansion cohort (Table 13).

Table 16: Summary of CRS events following dose delays in Study GCT3013-01 Expansion Patients with B-Cell NHL who did not receive Re-Priming

Duration	Delayed Dose	No CRS	Grade 1 CRS	Grade 2 CRS
CRS Following Dose Delays Less than or Equal to the Proposed Re-Priming Cut-Offs	**Step-up Dose 2 Delay** (n=0)	**≤8 days between step-up dose 1 and step-up dose 2** n/a*	n/a*	n/a*
	First Full Dose Delay (n=8)	**≤14 days between step-up dose 2 and first full dose** 50%	25%	25%
	Full Dose Delay	**≤42 days between full doses**		
	QW dosing (n=108)	93.5%	2.7%	3.7%
	Q2W dosing (n=43)	100%	0%	0%
	Q4W dosing (n=8)	100%	0%	0%
CRS Following Dose Delays Greater than the Proposed Re-Priming Cut-Offs	**Step-up Dose 2 Delay** (n=13)	**>8 days between step-up dose 1 and step-up dose 2** 92.3%	0%	7.7%
	First Full Dose Delay (n=2)	**>14 days between step-up dose 2 and first full dose** 0%	50%	50%
	Full Dose Delay	**>42 days between full doses**		
	QW, Q2W, or Q4W dosing (n=0)	n/a*	n/a*	n/a*

*not applicable.
Dose delay data is from 299 patients with B-cell NHL (i.e., LBCL, iNHL, aNHL, or MCL) in Study GCT3013-01 Expansion. Step-up dose 1 refers to the 0.16 mg dose with scheduled administration on Cycle 1 Day 1. Step-up dose 2 refers to the 0.8 mg dose with scheduled administration on Cycle 1 Day 8. First Full Dose refers to the first 48 mg dose with scheduled administration on Cycle 1 Day 15. 31Jan2022 data cut-off.
CRS = cytokine release syndrome; n = number of dose delay events; QW = once weekly; Q2W = every 2 weeks; Q4W = every 4 weeks.
Source: Generated based on data in listing L_fda_ir2_q6_delay1 in response to item 6 of 22Nov IR, Appendix 1, SDN 8; and listing L_fda_ir5_q4a_delay1 in response to 09Jan2023 IR, Appendix 1, SDN 15.

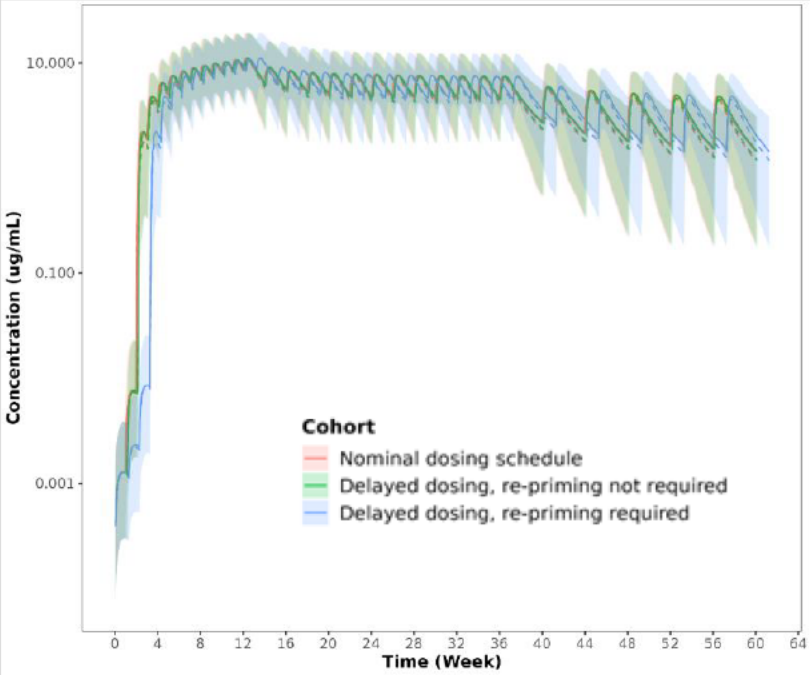
2) PopPK analysis indicates that when the dose delays were within the proposed dose delay cut-offs, epcoritamab concentration is not expected to fall below the C_{trough} obtained following the last step-up dose. Therefore, the proposed dose recommendations following dose delay do not put the patient at increased risk of CRS from potential resensitization to epcoritamab treatment. The re-priming recommendations in Table 15 maintain epcoritamab concentrations at or above the C_{trough} following the last step-up dose and adequately mitigate CRS. PopPK simulations

of exposure in 359 patients with B-cell NHL in GCT3013-01 and GCT3013-04 with popPK data evaluated different dose delay scenarios and are summarized below (refer to Figure 3, Figure 4, Figure 5, Figure 6, and Figure 7; and Table 17, Table 18, Table 19, Table 20, and Table 21).

Scenario 1 (delay/re-priming after step-up dose 1 of 0.16 mg epcoritamab):

- Simulation of scheduled dosing (reference).
- Simulation of step-up dose 2 (0.8 mg) given 8 days after step-up dose 1 (0.16 mg), followed by scheduled doses.
- Simulation where re-priming occurs 9 days after step-up dose 1 per Applicant's repriming strategy, followed by scheduled doses.

Figure 3: Simulated PK Profiles – Reference (Nominal Dosing Schedule) Compared to Dosing Delay After Step-Up Dose 1 With and Without Re-Priming (Scenario 1)



Solid line represents median of simulated individual PK profile. Dash line represents geometric mean of simulated individual PK profile. Shaded represents 5th to 95th percentile.
Source: Figure 4 in response to FDA 09 January 2023 information request, SDN 15

Table 17: Simulated Ctrough – Nominal Dosing Schedule Compared to Dosing Delay After Step-Up Dose 1 (Scenario 1)

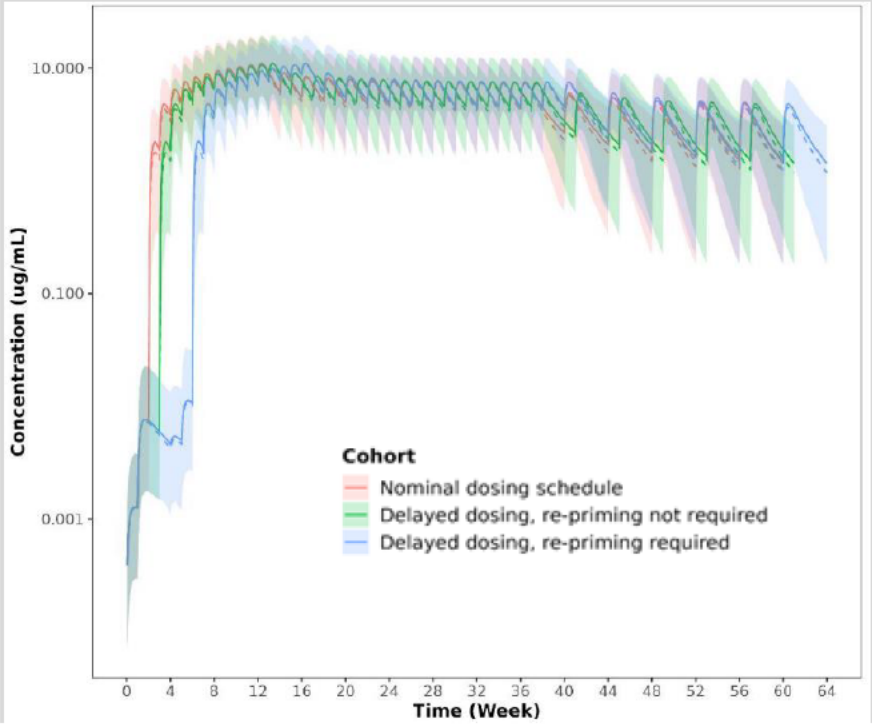
Simulated Cohort	Description	C_{trough} Following Step-Up Dose 1	
		Geo mean (ug/mL)	Geo mean 95% CI (ug/mL)
Nominal Dosing Schedule	7 days between step-up dose 1 (0.16 mg) and step-up dose 2 (0.8 mg)	0.00120	0.00110, 0.00130
Maximum Dose Delay without Required Re-priming	8 days between step-up dose 1 and step-up dose 2	0.00116	0.00107, 0.00126

Step-up dose 1 administered on Cycle 1 Day 1.
CI = confidence interval; C_{trough} = concentration immediately prior to next dose; geo mean = geometric mean.
Source: Reviewer analysis using dataset and model file provided by Applicant in response to 09 January 2023 information request

Scenario 2 (delay/re-priming after step-up dose 2 of 0.8 mg epcoritamab):

- Simulation of scheduled dosing (reference).
- Simulation of first full dose (48 mg) given 14 days after step-up dose 2 (0.8 mg), followed by scheduled doses.
- Simulation where re-priming occurs 21 days after step-up dose 2 per Applicant's repriming strategy, followed by scheduled doses.

Figure 4: Simulated PK Profiles – Reference (Nominal Dosing Schedule) Dosing Delay After Step-Up Dose 2 With and Without Re-Priming (Scenario 2)



Solid line represents median of simulated individual PK profile. Dash line represents geometric mean of simulated individual PK profile. Shaded represents 5th to 95th percentile.
Source: Figure 5 in response to FDA 09 January 2023 information request, SDN 15

Table 18: Simulated Ctrough –Nominal Dosing Schedule Compared to Dosing Delay After Step-Up Dose 2 (Scenario 2)

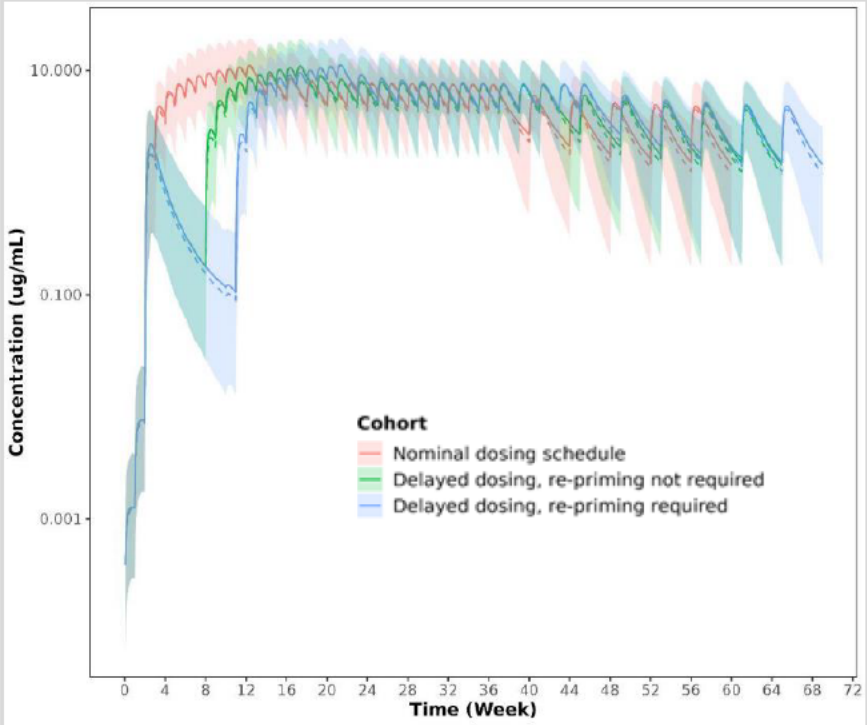
Simulated Cohort	Description	C_{trough} Following Step-Up Dose 2	
		Geo mean (ug/mL)	Geo mean 95% CI (ug/mL)
Nominal Dosing Schedule	7 days between step-up dose 2 (0.8 mg) and first full dose (48 mg)	0.00713	0.00657, 0.00773
Maximum Dose Delay without Required Re-priming	14 days between step-up dose 2 and first full dose	0.00554	0.00511, 0.00600

Step-up dose 2 administered on Cycle 1 Day 8.
CI = confidence interval; C_{trough} = concentration immediately prior to next dose; geo mean = geometric mean.
Source: Reviewer analysis using dataset and model file provided by Applicant in response to 09 January 2023 information request

Scenario 3 (delay/re-priming after a QW full dose of 48 mg epcoritamab):

- Simulation of scheduled dosing (reference).
- Simulation of second full dose given 6 weeks after first full dose, followed by scheduled doses.
- Simulation where re-priming occurs 7 weeks after first full dose per Applicant's repriming strategy, followed by scheduled doses.

Figure 5: Simulated PK Profiles – Reference (Nominal Dosing Schedule) Compared to Dosing Delay After First Full Dose With or Without Re-Priming (Scenario 3)



Solid line represents median of simulated individual PK profile. Dash line represents geometric mean of simulated individual PK profile. Shaded represents 5th to 95th percentile.
Source: Figure 6 in response to FDA 09 January 2023 information request, SDN 15

Table 19: Simulated Ctrough –Nominal Dosing Schedule Compared to Dosing Delay After First Full Dose (Scenario 3)

Simulated Cohort	Description	C_{trough} Following First Full Dose	
		Geo mean (ug/mL)	Geo mean 95% CI (ug/mL)
Nominal Dosing Schedule	7 days between first full dose and second full dose	1.52	1.39, 1.66
Maximum Dose Delay without Required Re-priming	42 days between first full dose and second full dose	0.154	0.140, 0.170

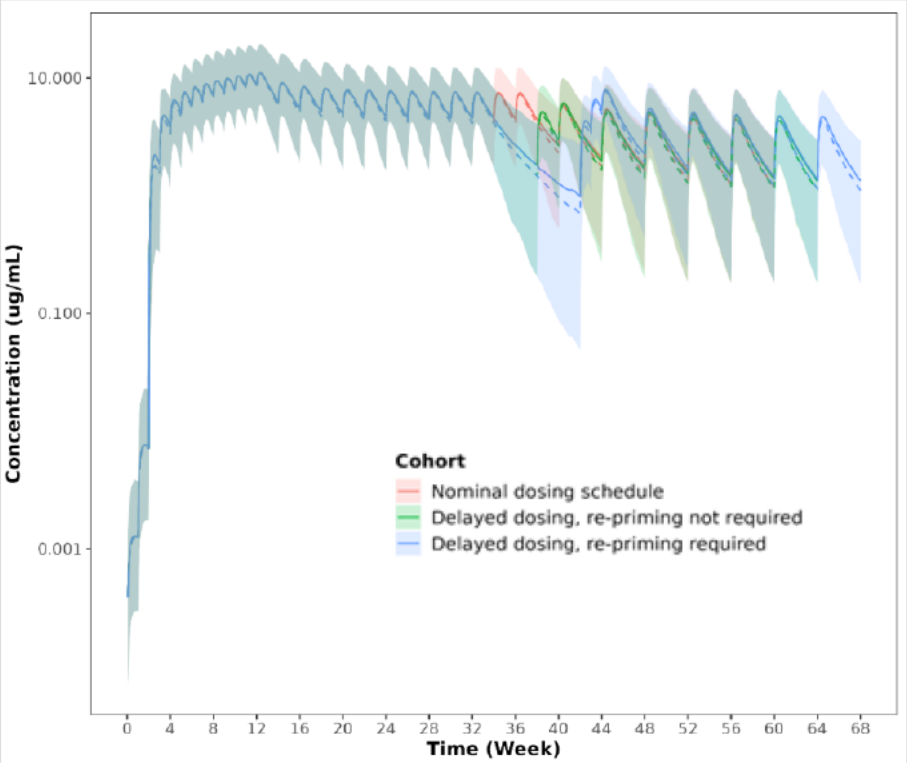
First full dose administered on Cycle 1 Day 15.
CI = confidence interval; C_{trough} = concentration immediately prior to next dose; geo mean = geometric mean.
Source: Reviewer analysis using dataset and model file provided by Applicant in response to 09 January 2023 information request

<u>Scenario 4 (delay/re-priming after a Q2W full dose of 48 mg epcoritamab):</u>

- Simulation of scheduled dosing (reference).
- Simulation of full dose (48 mg) given 6 weeks after full dose on Cycle 9 Day 1, followed by scheduled doses.

- Simulation where re-priming occurs 8 weeks after full dose on Cycle 9 Day 1 per Applicant's repriming strategy, followed by scheduled doses.

Figure 6: Simulated PK Profiles – Reference (Nominal Dosing Schedule) Compared to Dosing Delay During Q2W Dosing Window With or Without Re-Priming (Scenario 4)



Solid line represents median of simulated individual PK profile. Dash line represents geometric mean of simulated individual PK profile. Shaded represents 5th to 95th percentile.
Q2W = every 2 weeks.
Source: Figure 7 in response to FDA 09 January 2023 information request, SDN 15

Table 20: Simulated Ctrough –Nominal Dosing Schedule Compared to Dosing Delay During Q2W Dosing Window (Scenario 4)

Simulated Cohort	Description	C_{trough} Following Last Q2W Full Dose	
		Geo mean (ug/mL)	Geo mean 95% CI (ug/mL)
Nominal Dosing Schedule	14 days between Cycle 9 Day 1 full dose and the subsequent full dose	4.14	3.89, 4.42
Maximum Dose Delay without Required Re-priming	42 days between Cycle 9 Day 1 full dose and the subsequent full dose	1.47	1.33, 1.63

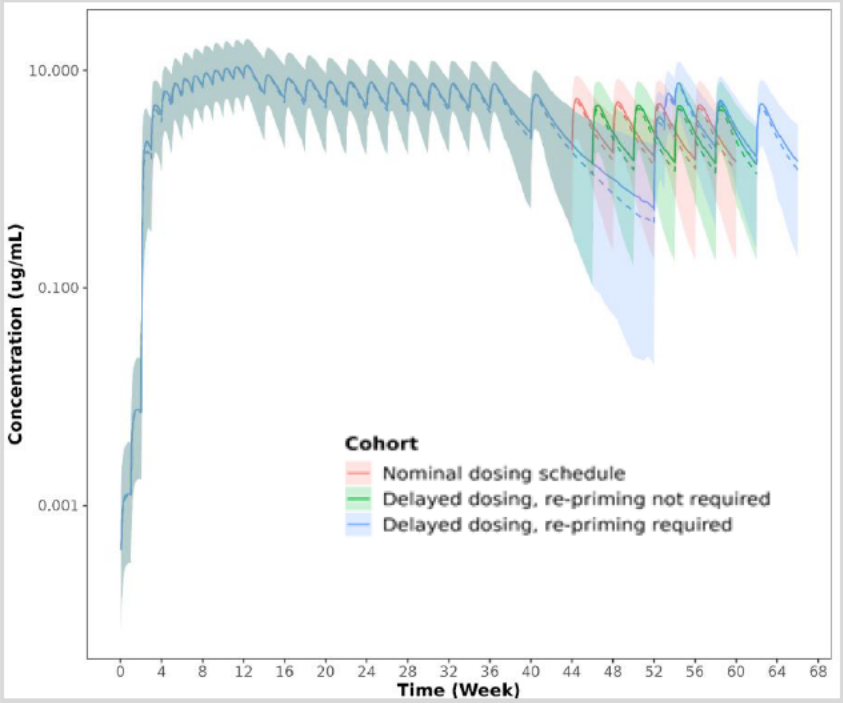
Last Q2W full dose administered on C9D1 for this scenario.
CI = confidence interval; C_{trough} = concentration immediately prior to next dose; geo mean = geometric mean; Q2W = every 2 weeks.

Source: Reviewer analysis using dataset and model file provided by Applicant in response to 09 January 2023 information request

Scenario 5 (delay/re-priming after a Q4W full dose of 48 mg epcoritamab):

- Simulation of scheduled dosing (reference).
- Simulation of full dose (48 mg) given 6 weeks after full dose on Cycle 12 Day 1, followed by scheduled doses.
- Simulation where re-priming occurs 10 weeks after full dose on Cycle 9 Day 1 per Applicant's repriming strategy, followed by scheduled doses.

Figure 7: Simulated PK Profiles – Reference (Nominal Dosing Schedule) Compared to Dosing Delay During Q4W Dosing Window With or Without Re-Priming (Scenario 5)



Solid line represents median of simulated individual PK profile. Dash line represents geometric mean of simulated individual PK profile. Shaded represents 5th to 95th percentile.
Q4W = every 4 weeks.
Source: Figure 8 in response to FDA 09 January 2023 information request, SDN 15

Table 21: Simulated Ctrough –Nominal Dosing Schedule Compared to Dosing Delay During Q4W Dosing Window (Scenario 5)

Simulated Cohort	Description	C_{trough} Following Last Q4W Full Dose	
		Geo mean (ug/mL)	Geo mean 95% CI (ug/mL)
Nominal Dosing Schedule	28 days between Cycle 11 Day 1 full dose and the subsequent full dose	1.78	1.62, 1.95
Maximum Dose Delay without Required Re-priming	42 days between Cycle 11 Day 1 full dose and the subsequent full dose	1.12	1.00, 1.25

Last Q4W full dose administered on C11D1 for this scenario.
CI = confidence interval; C_{trough} = concentration immediately prior to next dose; geo mean = geometric mean; Q4W = every 4 weeks.
Source: Reviewer analysis using dataset and model file provided by Applicant in response to 09 January 2023 information request

6.2.2.4. Outstanding Issues

Data:
N/A

The Applicant's Position:
No outstanding issues.

The FDA's Assessment:
FDA disagrees with the Applicant's assessment. The Agreed iPSP includes a deferral in patients ≥1 to 18 years with mature B-cell lymphoma for the completion of the population PK modeling study (refer to Section 10). Evaluation of clinical trial to confirm the appropriate dose and assess the PK, safety and preliminary efficacy in pediatric patients with mature B-cell lymphoma will be required as a PMR.

There is no PK data to assess the impact of racial categories other than White or Asian (refer to Section 6.2.2.2). PK and PD, in addition to safety and efficacy, of epcoritamab monotherapy should be further characterized in a population representative of the US patient population with large B-cell lymphoma. This will need to be evaluated as a PMC (Section 16).

6.3.Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Data:
The general pharmacology and PK characteristics of epcoritamab are summarized in Table 22.

Table 22: Applicant – General Pharmacology and Pharmacokinetic Characteristics of Epcoritamab

<table>
<tr><td colspan="2">PHARMACOLOGY</td></tr>
<tr><td>Mechanism of action</td><td>The activity of epcoritamab is dependent upon simultaneous engagement of CD20-expressing cancer cells and CD3-expressing endogenous T cells by epcoritamab that induces specific T-cell activation and T-cell-mediated killing of CD20-expressing cells, as epcoritamab does not have direct immune effector mechanisms.</td></tr>
<tr><td colspan="2">GENERAL INFORMATION</td></tr>
<tr><td>Maximum tolerated dose or exposure</td><td>A wide range of epcoritamab doses from 0.004 mg to 60 mg were explored in subjects with R/R B-NHL, including priming doses ranging from 0.004 to 0.16 mg, intermediate doses ranging from 0.25 to 1.6 mg, and full doses ranging from 0.0128 to 60 mg. None of the 29 subjects in the dose-determining set experienced DLTs in any of the dose levels tested (0.0128 to 60 mg), and a MTD was not identified.</td></tr>
<tr><td colspan="2">Bioanalysis</td></tr>
<tr><td>PK Bioanalytical assay</td><td>Epcoritamab concentrations quantified by a validated ECLIA-139 method were analyzed and presented in the documents for this submission.</td></tr>
<tr><td colspan="2">Pharmacokinetic (PK) Characteristics</td></tr>
<tr><td>Patient PK vs. healthy subject PK</td><td>No clinical studies to evaluate the PK in healthy subjects have been conducted with epcoritamab.</td></tr>
<tr><td>Steady-state exposure at the proposed dosing regimen</td><td>Concentrations appeared to approach or reach steady-state approximately 3 months after each QW, Q2W, or Q4W dosing regimen, respectively. Geometric mean AUC accumulation ratios were 9.54, 4.53, and 2.49 following QW, Q2W, and Q4W dosing, respectively. Geometric mean values of steady-state C_{max} were 10.8, 7.52, and 4.76 µg/mL following QW, Q2W, and Q4W dosing, respectively.

<u>The FDA's Assessment</u>:
Exposure parameters of epcoritamab in patients with relapsed or refractory LBCL are as follows:
<table>
<tr><th></th><th>C_{avg} (mcg/mL)[1]</th><th>C_{max} (mcg/mL)[1]</th><th>C_{trough} (mcg/mL)[1]</th></tr>
<tr><td>First full 48 mg dose</td><td>1.6 (72.4)</td><td>2.2 (70.0)</td><td>1.7 (74.0)</td></tr>
<tr><td>End of QW dosing (end of Cycle 3)</td><td>9.9 (45.1)</td><td>10.8 (41.7)</td><td>8.4 (53.3)</td></tr>
<tr><td>End of Q2W dosing (end of Cycle 9)</td><td>5.9 (49.3)</td><td>7.5 (41.1)</td><td>4.1 (73.9)</td></tr>
<tr><td>Steady state with Q4W dosing[2]</td><td>2.7 (69.5)</td><td>4.8 (51.6)</td><td>1.2 (130)</td></tr>
<tr><td colspan="4">[1] Values are geometric mean with geometric CV%
[2] Steady state values are approximated at Cycle 15 (Week 60)
Source: 3/27/23 Response to FDA recommended labeling change.</td></tr>
</table></td></tr>
<tr><td>Dose proportionality</td><td>Epcoritamab elimination showed nonlinear characteristics when</td></tr>
</table>

	evaluated using population PK modeling. As evident, exposure increases greater than dose-proportional for dosing regimens with the full dose <48 mg, and approximately dose-proportionally for dosing regimens with the full dose ≥48 mg. This indicates a possible plateau of tumor killing achieved for doses equal or exceeding 48 mg. The FDA's Assessment: Epcoritamab AUC increased more than proportionally over a full dosage range from 1.5 to 60 mg.
Accumulation	The geometric mean AUC accumulation ratios were 9.54, 4.53, and 2.49 following QW, Q2W, and Q4W dosing, respectively.
PK Variability	Moderate to high pharmacokinetic variability for epcoritamab was observed and characterized by inter-individual variability ranging from 25.7% to 137.5% coefficient of variation (CV) for epcoritamab PK parameters.
ABSORPTION	In absence of intravenous data, absolute bioavailability of SC administration cannot be estimated. Thus, all models were parameterized in terms of CL/F, Q/F, VC/F, and VP/F, where F is absolute bioavailability of SC administration. T_{max} was around 3 to 4 days (following the proposed SC full dose of epcoritamab 48 mg) The FDA's Assessment: The median (range) T_{max} of epcoritamab after the first full dose and end of the weekly dosing regimen (end of Cycle 3) treatment doses were 4.0 (0.3 to 7) days and 2.3 (0.3 to 3.2) days, respectively (Source: 3/27/23 Response to FDA recommended labeling change).
DISTRIBUTION	The geometric mean (CV%) central volume of distribution is 8.27 L (27.5%) in LBCL patients. FDA Assessment: The apparent volume of distribution is 25.6 L (82%) (Source: 3/27/23 Response to FDA recommended labeling change).
Metabolism	As an IgG1 Ab, epcoritamab is presumably biotransformed in the same manner as any other endogenous IgG (degraded into small peptides and amino acids via catabolic pathways), and is subject to similar elimination (Tabrizi et al., 2006; Mascelli et al., 2007).
ELIMINATION	The CL/F was 0.441 L/Day for LBCL subjects. The model-derived geometric mean half-life values according to washout period ranged from 22 to 25 days for the full dose of 48 mg. The FDA's Assessment: The apparent total clearance of approximately 0.53 L/day (40%) at the end of Cycle 3 is higher than the linear clearance (0.441 L/day) and more clinically relevant. The half-life was approximately 22 days (58%) for the full dose of 48 mg at the end

	of Cycle 3.
Immunogenicity	
	A total of 4 (2.5%) of 158 ADA-evaluable subjects with LBCL in the GCT3013 01 trial (ESC+EXP) who received epcoritamab at the proposed dosing regimen were ADA positive on treatment (but not at baseline), all with low titers. In the popPK analysis, no meaningful differences in PK were detected between ADA-negative and ADA-positive subjects. The ADA data, although limited, showed no evidence of ADA impact on efficacy, safety and tolerability in ADA-positive subjects. Overall, the low number of subjects with ADAs observed suggests a low risk for immunogenicity with epcoritamab using the proposed dosing regimen. The FDA's Assessment: Anti-epcoritamab antibodies developed in 2.6% of patients (4 of 156) treated with epcoritamab at 0.16/0.8/48 mg RP2D dosage in LBCL cohort in Study GCT3013-01 (up to 10 cycles). Because of the low occurrence of anti-epcoritamab antibodies, the effect of these antibodies on the PK, pharmacodynamics, safety, and effectiveness of epcoritamab is unknown
Drug interaction	
	Epcoritamab causes transient and modest release of cytokines that may potentially suppress CYP450 enzymes. Upon initiation of epcoritamab therapy, therapeutic monitoring in patients being treated with CYP450 substrates with a narrow therapeutic index should be considered. Modest peak IL-6 concentrations were observed on C1D16 (following administration of the first full dose of 48 mg on C1D15) in subjects with LBCL in the aNHL expansion cohort of the GCT3013-01 trial. The risk of drug interactions is considered low. The FDA's Assessment: Cytokine release induced by epcoritamab may suppress activity of CYP enzymes, resulting in increased exposure of CYP substrates. Cytokine release increases after the first dose of epcoritamab on Cycle 1 Day 1, reached peak levels after the first 48 mg dose on Cycle 1 Day 15, and returned to baseline prior to the next 48 mg dose on Cycle 1 Day 22. 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 on Cycle 1 Day 15 and during and after CRS.
Pharmacodynamic (PD) Characteristics	
Pharmacodynamics	Pharmacodynamics of B cells, T cells and cytokines were studied. See Section 6.2.1. The FDA's Assessment: *Circulating B Cell Count*

	Circulating B cells decreased to undetectable levels (<10 cells/microliter) after administration of the approved recommended dosage of epcoritamab in patients who had detectable B cells at treatment initiation by Cycle 1 Day 15 (after the first full dose of 48 mg) and the depletion was sustained while patients remained on treatment. *Cytokine Concentrations* Transient elevation of circulating cytokines (IL-2, IL-6, IL-10, TNF-α, and IFN-γ) was observed at dose levels of 0.04 mg and above. After administration of the approved recommended dosage of epcoritamab, the cytokine levels increased within 24 hours after first dose on Cycle 1 Day 1, reached maximum levels after the first 48 mg dose on Cycle 1 Day 15, and returned to baseline prior to the next 48 mg full dose on Cycle 1 Day 22.
QT/QTc prolongation	At the arithmetic mean predicted C_{max} value of 11.7 µg/mL following the proposed dosing regimen QW doses, QTcF prolongation was predicted to be 0.76 msec, with the 95% CI upper bound of 3.40 msec. Based on the available data, epcoritamab does not cause QT prolongation based on the lack of relationship between epcoritamab PK and ΔQTcF, the lack of a biologic mechanism for epcoritamab to directly impact QTcF, and the clinical safety findings that epcoritamab did not have a clinically relevant effect on cardiac repolarization or result in clinically meaningful cardiac TEAEs.

Abbreviations: Ab = antibody; ADA = anti-drug antibody; B-NHL = B-cell non-Hodgkin lymphoma; CL = clearance; CV% = coefficient of variation; DLT = dose-limiting toxicity; ESC = escalation; EXP = expansion; LBCL = large B-cell lymphoma; MTD = maximum tolerated dose; PK = pharmacokinetics; Q2W = once every 2 weeks; Q4W = once every 4 weeks; QW = once weekly; R/R = relapsed or refractory; T_{max} = time to reach maximum concentration.

The Applicant's Position:

The pharmacology and clinical pharmacokinetics support the BLA for epcoritamab in patients with R/R LBCL after 2 or more lines of systemic therapy. Overall, the PK of epcoritamab is well characterized by the popPK model. The incidence of antibodies to epcoritamab was low with all positive subjects having low titers. There was no evidence to suggest that positive ADA status had an impact on epcoritamab exposure, safety, or efficacy. Additionally, the risk of drug interactions is considered low.

The FDA's Assessment:

The FDA generally agrees with the Applicant's position. Refer to the FDA's Assessment in Table 22 above for FDA comments and recommendations.

6.3.2. Clinical Pharmacology Questions

6.3.2.1 Does the clinical pharmacology program provide supportive evidence of effectiveness?

Data:

Clinical Data

Overall evidence of efficacy is demonstrated by the clinical results seen in subjects enrolled in the pivotal aNHL expansion cohort of Study GCT3013-01. As of a 31 Jan 2022 data cutoff date, in the 157 subjects with LBCL included in the Full Analysis Set, the ORR was 63.1% (95% CI: 55.0, 70.6) and the CR rate was 38.9% (95% CI: 31.2, 46.9) as assessed by IRC using Lugano criteria. Responses were durable. After a median follow-up of 10.7 months (range: 0.3, 17.9), the median DOR in all responders was 12.0 months (95% CI: 6.6, NR) and the median DOR in complete responders was not reached (95% CI: 12.0, NR). Fifty-one (32.5%) subjects were continuing to receive treatment as of the 31 Jan 2022 data cutoff date.

Pharmacodynamics:

The proposed mechanism of action of epcoritamab is induction of T-cell-mediated cytotoxicity of CD20-expressing cells with associated T-cell activation and proliferation, upon simultaneous binding to CD20 on lymphoma cells and CD3 on T cells.

In subjects who had detectable peripheral B-cells at treatment initiation, epcoritamab induced depletion of circulating B cells (defined as CD19 B-cell counts <10 cells/µl in subjects who have detectable B cells at treatment initiation) after the first full dose (48 mg), which was sustained while subjects remained on treatment.

A transient decrease in circulating T cells was observed within 6 to 14 hours after the initial priming dosing of epcoritamab (0.16 mg on C1D1). The level of T cells rapidly returned to baseline, consistent with T cell margination that has been reported for other CD3 T cell-redirecting antibodies (Nagele et al., 2017). Subsequent treatment with epcoritamab induced expansion and activation of circulating T cells from baseline, consistent with the proposed mechanism of action.

Exposure-Response:

The exposure-response analysis for efficacy of epcoritamab is presented in Section 6.3.2.2.

The Applicant's Position:

The clinical pharmacology program provides supportive evidence of epcoritamab effectiveness in patients with R/R LBCL after 2 or more lines of systemic therapy. Depletion of circulating peripheral B cells, transient decrease in T cells, and subsequent T cell expansion and activation are consistent with the proposed mode of action of epcoritamab. The clinical efficacy data provide strong evidence of epcoritamab effectiveness. The exposure-response analysis for efficacy provides further supportive evidence for effectiveness.

The FDA's Assessment:
The FDA agrees with the Applicant's position that clinical pharmacology analyses support evidence of efficacy following the proposed dosage regimen. For details regarding the assessment of the full dose, refer to Section 19.4.5.2 for assessment based on E-R analysis for efficacy and PK/PD analyses for efficacy. Refer to Section 6.2.2.1**Error! Reference source not found.** for details regarding the justification of the full dose based on maintenance or improvement in response when transitioning from QW to Q2W to Q4W dosing intervals.

6.3.2.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Data:
A wide range of epcoritamab doses, ranged from 0.004 mg to 60 mg, were explored in subjects with R/R B-NHL, including priming doses ranging from 0.004 to 0.16 mg, intermediate doses ranging from 0.25 to 1.6 mg, and full doses ranging from 0.0128 to 60 mg.
Clinical efficacy data suggest that treatment with epcoritamab using the dosing regimen of 0.16 mg priming, 0.8 mg intermediate, and 48 mg full dose resulted in clinically meaningful, deep, and durable responses in subjects with R/R LBCL in both GCT3013-01 and GCT3013-04 (Section 8.1.7). Overall, the safety profile of epcoritamab at this proposed dosing regimen is considered manageable with appropriate monitoring and mitigation measures in adult patients with R/R LBCL after two or more lines of systemic therapy (Section 8.2.11.). With the proposed dose regimen, eighty-four (50.3%) subjects in the Safety Pool 01 LBCL group (n=167) experienced at least 1 CRS event. The median time to first CRS onset was 16.0 days (range, 1, 55), generally following administration of the first full dose of 48 mg epcoritamab on C1D15. Most subjects had a maximum grade 1 event (52 subjects; 31.1%), with 28 (16.8%) subjects having a maximum grade 2 event and 4 (2.4%) subjects having a maximum grade 3 event. No grade 4 or grade 5 events of CRS occurred. Tocilizumab, which was administered to subjects to manage CRS, was given to 25 (15.0%) subjects. Full discussion of the incidence of CRS is presented in Section 8.2.5.

Analysis data for priming/intermediate doses:
The proposed priming (0.16 mg) and intermediate (0.8 mg) doses of epcoritamab resulted in similar or numerically lower incidence of ≥grade 2 CRS during the first cycles (following priming, intermediate, the first and second full dose periods) compared to the other dose regimens studied in the Dose Escalation Part of the GCT3013-01 trial, indicating that these proposed priming and intermediate doses of epcoritamab were effective in reducing CRS in subjects with LBCL (Module 2.7.2 Figure 24). The proposed 0.16 mg priming dose and 0.8 mg intermediate dose of epcoritamab produced similar or numerically lower peak IL-6 concentrations compared with the other priming and intermediate doses tested in the Dose Escalation Part of the GCT3013-01 trial (Module 2.7.2 Figure 25).
A diminishing relationship between IL-6 peak concentration and CRS incidence over time was

observed, which provides strong evidence that that the proposed step-up dosing regimen (ie, 0.16 mg priming/0.8 mg intermediate doses) attenuated the incidence of CRS (Module 2.7.2 Figure 28).

Analysis data for 48 mg full dose:

Exposure-Response Relationship for Clinical Safety

No increasing trends were observed between PK and AEs (≥ grade 3 TEAE, serious TEAE, ≥ grade 3 neutropenia (TEAE), ≥ grade 3 infections (TEAE), injection site reactions, TEAE leading to dose delay, TEAE leading to treatment discontinuation, any grade CRS, ≥ grade 2 CRS, CRS requiring tocilizumab, ICANS, and CTLS) within the epcoritamab exposure range studied (Table 23). Additional details of exposure-safety analyses are presented in Module 2.7.2 Section 3.3.2.

Table 23: Frequencies of Adverse Events, by Exposure Tertiles– GCT3013-01 Escalation + Expansion (PK-Evaluable Subjects at All Dose Levels in Escalation Part)

	R/R LBCL (N=195) n (%)			R/R DLBCL (N=176) n (%)		
Exposure (Cycle 1 AUC) Tertile (N)	**Tertile 1 N=65**	**Tertile 2 N=65**	**Tertile 3 N=65**	**Tertile 1 N=59**	**Tertile 2 N=58**	**Tertile 3 N=59**
Exposure range (μg/mL·day)	0.0021; 28	28; 47.5	48; 101	0.0021; 28	28.2; 47.2	48; 101
AE type						
≥grade 3 TEAE	52 (80%)	34 (52.3%)	41 (63.1%)	46 (78%)	30 (51.7%)	38 (64.4%)
Serious TEAE	46 (70.8%)	29 (44.6%)	39 (60%)	42 (71.2%)	26 (44.8%)	36 (61%)
≥grade 3 neutropenia (TEAE)	16 (24.6%)	14 (21.5%)	16 (24.6%)	13 (22%)	12 (20.7%)	15 (25.4%)
≥grade 3 infections (TEAE)	17 (26.2%)	5 (7.7%)	14 (21.5%)	15 (25.4%)	4 (6.9%)	12 (20.3%)
Injection site reactions	24 (36.9%)	18 (27.7%)	25 (38.5%)	20 (33.9%)	17 (29.3%)	25 (42.4%)
TEAE leading to treatment discontinuation	12 (18.5%)	5 (7.7%)	2 (3.1%)	12 (20.3%)	4 (6.9%)	2 (3.4%)
TEAE leading to dose delay/interruption	24 (36.9%)	26 (40%)	20 (30.8%)	21 (35.6%)	22 (37.9%)	19 (32.2%)
CRS any grade	39 (60%)	25 (38.5%)	40 (61.5%)	36 (61%)	20 (34.5%)	37 (62.7%)
CRS ≥grade 2	22 (33.8%)	8 (12.3%)	13 (20%)	18 (30.5%)	7 (12.1%)	13 (22%)
CRS treated with tocilizumab	20 (30.8%)	4 (6.2%)	9 (13.8%)	16 (27.1%)	4 (6.9%)	9 (15.3%)
ICANS (All grade)	1 (4.2%)	3 (4.9%)	4 (6.7%)	1 (4.5%)	2 (3.7%)	4 (7.4%)
CTLS (All grade)	2 (3.1%)	0 (0%)	0 (0%)	1 (1.7%)	0 (0%)	0 (0%)

Abbreviations: AE = adverse event; AUC = area under the concentration-time curve; CRS = cytokine release syndrome; CTLS = clinical tumor lysis syndrome; DLBCL = diffuse large B-cell lymphoma; ICANS = immune effector cell-associated neurotoxicity syndrome; LBCL = large B-cell lymphoma; N = number of subjects; R/R = relapsed or refractory; TEAE = treatment-emergent adverse event.
Missing values were removed from summaries.
Source: PopPK Report Table 9

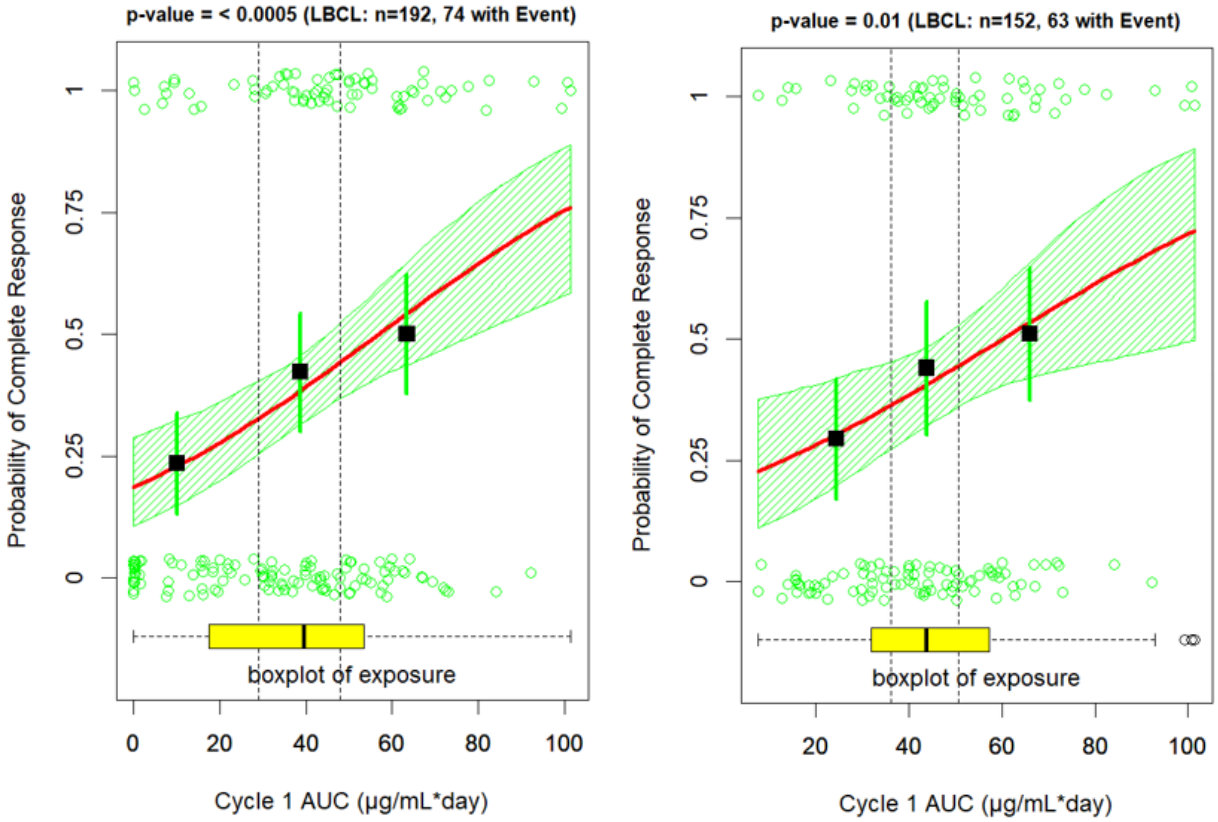
Exposure-Response Relationship for Clinical Efficacy:

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

At the proposed 48 mg full dose (ie, analysis using data only from 48 mg full dose level), exposure-efficacy relationships remained positive for all the key efficacy endpoints and were statistically significant ($p<0.05$) for CR rate (Figure 8). These results indicate that full doses <48 mg are likely to result in compromised efficacy.

Target-mediated drug disposition saturation was observed starting from 48 mg, due to a plateau in tumor killing. In addition, less significant exposure-efficacy relationships were observed when data from the 48 mg dose alone were analyzed when compared to data from across all doses. The exposure-efficacy relationships for ORR, PFS, and OS are no longer statistically significant using 48 mg data alone. Therefore, full doses >48 mg are not expected to lead to significantly higher efficacy. Additional details of exposure-efficacy analyses are presented in Module 2.7.2 Section 3.3.1.

Figure 8: Applicant – Logistic Regression for Complete Response: GCT3013-01 (Left, Data from Subjects Administered Any Full Dose) and GCT3013-01 (Right, Data from Subjects Administered Full Dose of 48 mg Alone)



Abbreviations: AUC = area under the concentration-time curve; DLBCL = diffuse large B-cell lymphoma; LBCL = large B-cell lymphoma; n = number of subjects.
Left: LBCL; right: DLBCL. The red solid line and green shaded area represent the logistic regression model prediction and 95% confidence interval of predictions. Points show exposure of individual subjects with events (p=1) and without events (p=0). Black squares and vertical green lines show observed fraction of subjects with events in each exposure group and 95% confidence interval for these fractions. Dashed vertical lines show bounds of exposure groups. Box plot of exposure is shown by the yellow box with whiskers.
Source: PopPK Report Figure 103 and 104

The Applicant's Position:

Based upon the popPK and exposure-response analyses using data from the GCT3013-01 and GCT3013-04 trials, the proposed priming (0.16 mg) and intermediate (0.8 mg) doses of epcoritamab represents a step-up dosing regimen that mitigates the incidence of ≥grade 2 CRS, in subjects with R/R (D)LBCL. In addition, the proposed full dose (48 mg) of epcoritamab is appropriate in the (D)LBCL patient population, providing significantly better efficacy with a manageable safety profile when compared to lower doses. Decreasing the full dose of epcoritamab is likely to result in compromised efficacy, without improvement of the benefit-

risk profile. Furthermore, higher epcoritamab doses (ie, 60 mg) may not lead to significantly higher efficacy, in subjects with R/R (D)LBCL. Thus, the overall data package supports the proposed dosing regimen of a 0.16 mg priming dose, 0.8 mg intermediate dose, and 48 mg full dose in this patient population.

The FDA's Assessment:
The FDA agrees with the Applicant's position that the proposed dose and schedule of 0.16/0.8/48 mg for epcoritamab is appropriate for the general population for which the indication is being sought. See detailed discussion in Section 6.2.2.1.

Full doses lower than the proposed full dose of 48 mg will likely have lower ORR and CR rates. However, due to limited efficacy data at higher full doses, it is unclear if clinical efficacy would differ following full doses higher than 48 mg QW compared to the proposed dosage regimen (0.16/0.8/48 mg). Refer to Section 19.4.5.2**Error! Reference source not found.** for detailed r eview of the E-R efficacy analyses.

6.3.2.3 Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors (e.g. race, ethnicity, age, performance status, genetic subpopulations, etc.)?

Data:
A comparison of AUC during Cycle 1 by intrinsic factors is presented in Figure 9. Intrinsic factors examined included body weight, age, sex (at birth), race (Asian, white, and other), ADA (status and titer), baseline renal function, baseline hepatic function, ECOG performance status, baseline disease characteristics (including Ann Arbor Stage, tumor size, lymphoma subtype), and baseline albumin.
Subgroup size for ethnicity (≤1.2% Hispanic or Latino) precluded analysis of the influence of ethnicity on epcoritamab exposure by ethnicity
Body Weight:
Body weight was the main covariate identified that had a significant effect on epcoritamab PK. The covariate analysis indicated a statistically significant effect of body weight on both linear clearance and central volume of distribution of epcoritamab. When compared to the AUC in subjects who weighed 65 to <85 kg, the average AUC during Cycle 1 was 10.6% lower in subjects who weighed ≥85 kg and 47.6% higher in subjects with weight <65 kg. Since efficacy and safety were generally consistent across body weight categories (Figure 11 and Section 8.2.7, respectively), the difference in exposures among different weight groups is considered not clinically meaningful. As a result, flat dosing of epcoritamab (ie, no adjustment for body weight) is proposed.
Sex
Sex at birth (male n=195; female n=132) did not have a statistically significant effect on the PK

of epcoritamab after accounting for body weight. Slightly higher exposure was observed in female subjects (AUC_{Cycle1} higher by 24.6%), which can be attributed to 16.6% lower mean body weight. No clinically meaningful differences in efficacy or safety in subgroups by sex were observed (Figure 11 and Section 8.2.7, respectively).

Age

Age (20 to 89 years) was a statistically significant covariate on the absorption rate constant but did not influence other PK parameters. Comparison of epcoritamab exposure among subjects <65 years (n=133), 65 to <75 years (n= 127), and ≥75 years (n=67) did not show any meaningful differences or age-related trends. No clinically meaningful differences in efficacy or safety in subgroups by age were observed.

Race

Race (white [n=185], Asian [n=99], or other [n=43]) did not have a statistically significant effect on epcoritamab PK after accounting for body weight. Compared with white subjects, epcoritamab exposure (AUC_{Cycle1}) was 35.2% higher in Asian subjects, while "other" subjects had similar exposure to white subjects. (geometric mean body weight of 61.1 kg vs 78.2 kg), the exposure difference between white and Asian was mainly attributable to body weight.

No clinically meaningful differences in efficacy in subgroups by race were observed. There were no apparent race-related trends in the frequency and severity of events across TEAE categories, except for serious TEAEs, and the AESI of CRS. White subjects had a higher incidence of serious TEAEs compared to Asian and other subgroups (63.2% vs 43.7% and 48.4%, respectively). Asian subjects had a higher incidence of CRS compared to white and other subgroups (76.1% vs 51.9% and 32.3%), but differences in incidence of grade 3 CRS were not as large (7.0% vs 2.8% and 0%, respectively). These observations are not likely to be due to differences in epcoritamab exposure since exposure-safety analyses suggest that there is no apparent relationship between epcoritamab PK and serious TEAEs or CRS (all grade or grade 2 or higher).

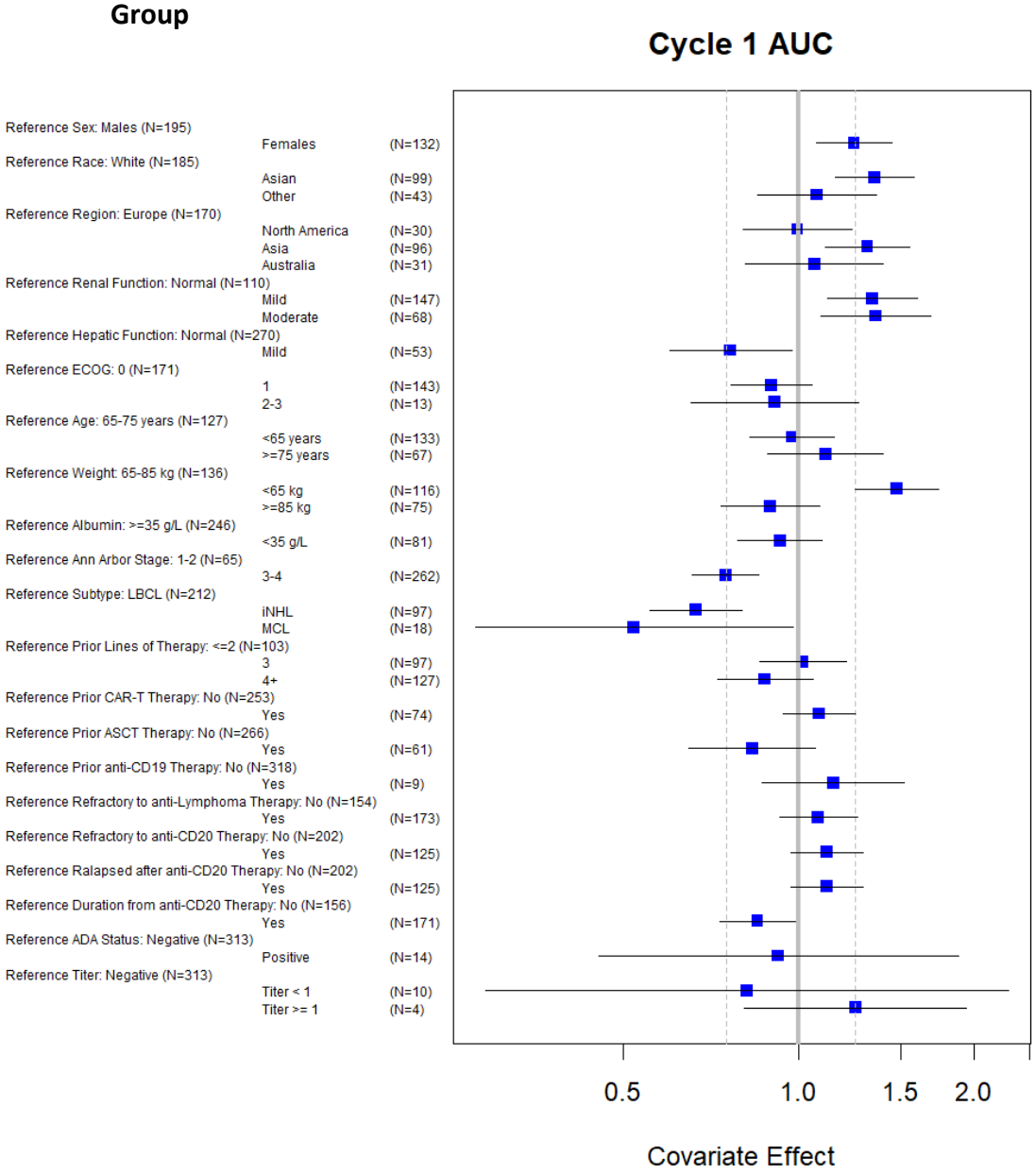
Baseline Renal Impairment

Mild and moderate renal impairment did not have a significant effect on epcoritamab PK after accounting for body weight. The assessment of renal impairment was based on estimated CrCl at baseline as determined using the Cockcroft-Gault formula. The exposure (AUC_{Cycle1}) in subjects with mild (<90 mL/min; n=147) and moderate (≥30 to <60 mL/min; n=68) renal impairment was approximately 33.9% to 35.7% higher compared with subjects who had normal renal function (CrCl ≥90 mL/min; n=115). This difference is consistent with the differences in body weight between these subgroups.

A trend toward higher incidence for all grade CRS corresponding to increased renal impairment (normal, mildly impaired, moderately impaired) was observed in LBCL subjects in Safety Pool 01 (44.3% vs 55.1% vs 60.0%, respectively). However, subjects who had mild or moderate renal impairment did not appear to have a notably increased incidence of grade ≥3 TEAEs, including CRS. A trend toward higher incidence of serious TEAEs corresponding to increased renal impairment (normal, mildly impaired, moderately impaired) was also observed in LBCL subjects in Safety Pool 01 (52.9% vs 60.9% vs 68.0%, respectively). Results may be confounded by the

potential for increased disease severity in subjects with impaired renal function and should be interpreted with caution.
Based upon results from the exposure-safety analysis, incidence of serious TEAEs did not increase with increasing epcoritamab exposure. Therefore, the observed differences in TEAEs are unlikely due to epcoritamab exposure.
Epcoritamab has not been studied in subjects with severe renal impairment to end-stage renal disease (CrCl <30 mL/min).
Baseline Hepatic Impairment
The effect of hepatic impairment on epcoritamab exposure in subjects who had mild hepatic impairment (total bilirubin ≤ULN and AST >ULN, or total bilirubin 1 to 1.5×ULN and any AST, as defined using the NCI criteria of hepatic dysfunction; n=53) compared with subjects who had normal hepatic function (total bilirubin and AST ≤ULN; n=270) was assessed using the popPK model. One (0.3%) subject had moderate hepatic impairment (total bilirubin >1.5 to 3.0×ULN and any AST), an insufficient number to evaluate the exposure in this subpopulation; exposure in that subject was similar to that of subjects with normal hepatic function. No subjects had severe hepatic impairment (total bilirubin >3×ULN and any AST) and 3 subjects had missing values of hepatic function.
Some trends toward higher incidences across TEAE categories and the AESIs of CRS and ICANS were observed, with differences ≥5% between subgroups noted. Results may be confounded by the potential for increased disease severity in subjects with impaired hepatic function and differences should be interpreted with caution.
The epcoritamab exposure (AUC_{Cycle1}) in subjects with mild hepatic impairment was 23.6% lower than that in subjects with normal hepatic function. The trends toward higher incidence of TEAEs in subjects with mild hepatic impairment is unlikely to be due to differences in epcoritamab exposure since epcoritamab exposure was lower in these subjects. Based on the available data no dose adjustment is warranted for subjects with baseline mild hepatic impairment.
The impact of moderate or severe hepatic impairment (total bilirubin >1.5×ULN and any AST) on epcoritamab exposure and activity is unknown.
Additional Factors:
in addition, ECOG performance status, Ann Arbor stage, and lymphoma subtype (LBCL or DLBCL) had minimal effect on exposure. Baseline disease burden in subjects did not affect epcoritamab PK.

Figure 9: Applicant – Predicted Epcoritamab Cycle 1 AUC by Covariates, Relative to Reference Group



Abbreviations: ADA = antidrug antibodies; ASCT = autologous stem cell transplant; AUC = area under the concentration-time curve; CAR-T = chimeric antigen receptor T cell; CD = cluster of differentiation; ECOG = Eastern Cooperative Oncology Group; LBCL = large B-cell lymphoma; N = number of subjects.
Source: popPK/Figure 9

The Applicant's Position:

No dose adjustments are recommended based on intrinsic patient factors.

The FDA's Assessment:

Disclaimer: In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

The FDA agrees with Applicant's position that there is no need for dose adjustment for the currently proposed indication (i.e., epcoritamab 0.16/0.8/48 mg monotherapy dosage in patients with R/R LBCL) according to body weight, age, sex, Asian or White racial category, mild to moderate renal impairment, or mild hepatic impairment. Refer to the detailed discussion in Section 6.2.2.2.

6.3.2.4 Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Data:
Epcoritamab causes transient and modest release of cytokines that may potentially suppress CYP450 enzymes. Modest peak IL-6 concentrations were observed on C1D16 (following administration of the first full dose of 48 mg on C1D15) in subjects with LBCL in the aNHL expansion cohort of the GCT3013-01 trial. In addition, an exploratory safety assessment in 4 subjects who received sensitive CYP450 substrates with a narrow therapeutic index within 2 weeks of a CRS episode showed no apparent difference in rates of grade 3 and 4 TEAEs compared to the overall population (Module 2.7.4 Table 3.19) Therefore, the risk of drug interactions is considered low.

The Applicant's Position:
Based on the data from the GCT3013-01 and GCT3013-04 trials, the risk of drug interaction due to CRS is considered low for epcoritamab. Upon initiation of epcoritamab therapy, therapeutic monitoring in patients being treated with sensitive CYP450 substrates with a narrow therapeutic index should be considered.
Given the technical challenges of conducting a dedicated drug-drug interaction study to coincide with the peak of cytokine release and expected variance in degree of cytokine increase for individual patients, no formal drug-drug interaction study is considered feasible to assess the drug interaction potential due to cytokine release after epcoritamab treatment.

The FDA's Assessment:
Epcoritamab can cause transient release of cytokines that may potentially suppress CYP450 enzymes. Based on evaluation of the totality of data, FDA considers the risk of drug interactions to be low. FDA's conclusion is based on the following considerations:

- The elevations of cytokines observed after epcoritamab doses are transient in nature and attenuate with repeat dosing.
- The highest drug-drug interaction risk is expected to occur from initiation of epcoritamab step-up dosing schedule up to 14 days after the first full dose (48 mg) on Cycle 1 Day 15, and during and after CRS. Refer to Section 19.4.2 for analysis.

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Primary Reviewer Team Leader

Disclaimer: In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

7 Sources of Clinical Data

7.1. Table of Clinical Studies

Data:

An overview of clinical studies supporting the efficacy and safety of epcoritamab is presented in Table 24. PK and ADA data from both GCT3013-01 and GCT3013-04 are as of a 30 Nov 2021 data cutoff date. Other data, including safety and efficacy, are as of a 31 Jan 2022 data cutoff date.

Table 24: Applicant – Clinical Studies Supporting the Efficacy and Safety of Epcoritamab

Trial Identity: GCT3013-01; NCT03625037	
Trial Design	Phase 1/2, first-in-human, open-label, dose escalation/ expansion
Regimen/ schedule/ route	Dose Escalation Part: Epcoritamab was administered subcutaneously in 28-day cycles: weekly in C1-2, every other week in C3-6, and every 4 weeks from C7 onwards. Epcoritamab was assessed in 17 different step-up dosing regimens prior to selection of RP2D; in C1, regimens comprised priming (0.004 – 0.16 mg) on D1; intermediate (0.25 – 1.6 mg) on D8; and full doses (0.0128 – 60 mg) on D15 and D22, followed by full doses administered in 28-day cycles: weekly in C2; every other week in C3-6; and every 4 weeks from C7 onwards. Expansion Part: Epcoritamab was administered subcutaneously at the selected RP2D in 28-day cycles, starting with step-up dosing in C1 (priming 0.16 mg on D1, intermediate 0.8 mg on D8, and full 48 mg on D15 and D22), and 48 mg full dose weekly in C2-3, every other week in C4-9, and every four weeks from C10 onwards.
Study Endpoints	Dose Escalation Part: DLTs, AEs, cytokine measures, laboratory parameters, Pk parameters, immunogenicity, anti-lymphoma activity (ORR, CR, and PR, per Lugano criteria), DOR, PFS, TTNT, and OS. Expansion Part: ORR, DOR, CR rate, DOCR, PFS, and TTR per Lugano criteria as assessed by IRC; OS; TTNT; and rate of MRD negativity; safety, as measured by AEs, laboratory parameters, hospitalizations, and cytokine measure; PK parameters and incidence of ADAs to epcoritamab; and changes in FACT-Lym scores.
Treatment Duration/ Follow Up	Until disease progression unless the subject fulfilled one of the discontinuation criteria. All AEs were reported until the safety follow-up visit, which occurred 60 days after the last epcoritamab dose. Survival was assessed at least every 3 months after last administration of epcoritamab and continue until the subject died or withdrew from the trial.
No. of patients enrolled	Dose Escalation Part: N=68 (12 subjects received the 48 mg full dose). aNHL Expansion: N=157 (139 with DLBCL; 18 with other aNHL) iNHL Expansion: N=105, including 92 subjects in the FL Grade 1-3a Cohort, and 13 subjects in the Other iNHL Cohort (9 subjects with MZL, 3 subjects with SLL, and 1 subject with DLBCL (protocol deviation) (enrollment ongoing) MCL Expansion: N=37 (enrollment ongoing)
Study Population	Subjects with relapsed, progressive, and/or refractory B-cell lymphoma. Subjects in the Dose Escalation Part of this trial had CD20+ mature B-cell neoplasm following treatment with an anti-CD20 mAb-containing regimen and/or relapsed after autologous stem cell rescue and had exhausted or were ineligible for all standard therapeutic options. Subjects in the Expansion Part of this trial had been previously treated with at least 2 lines of systemic antineoplastic therapy including at least 1 anti-CD20 mAb-containing therapy.
No. of Centers and Countries	Dose Escalation: 10 sites across 4 countries aNHL Expansion: 54 sites across 13 countries

	MCL Expansion: 20 sites across 9 countries iNHL Expansion: 48 sites across 12 countries
Trial Identity: GCT3013-04; NC04542824T	
Trial Design	Phase 1/2, open-label, dose-escalation/ expansion
Regimen/ schedule/ route	Dose Escalation Part: Epcoritamab was administered subcutaneously in 28-day cycles; step-up dosing assessed in C1, comprising priming (0.16 mg) on D1; intermediate (0.8 mg) on D8; and full doses of either 24 or 48 mg on D15 and D22, followed by full doses weekly in C2-3, every other week in C4-9, and every 4 weeks from C10 onwards. Expansion Part: Epcoritamab was administered subcutaneously at the selected RP2D regimen in 28-day cycles; step-up dosing assessed in C1, comprising priming (0.16 mg) on D1; intermediate (0.8 mg) on D8; and full (48 mg) on D15 and D22, followed by 48 mg full doses weekly in C2-3, every other week in C4-9, and every 4 weeks from C10 onwards.
Study Endpoints	Dose Escalation Part: DLTs, AEs, cytokine measures, laboratory parameters, PK parameters, incidence of ADAs; ORR, CR rate, DOR, and PFS as determined by Lugano criteria and LYRIC; TTNT; and OS. Expansion Part: ORR, CR rate, DOR, PFS, DOCR, TTCR, and TTR based on IRC assessment determined by Lugano criteria; TTNT; OS; safety, as assessed by AEs, laboratory parameters, and cytokine measures; PK parameters and incidence of ADAs; and rate and duration of MRD negativity.
Treatment Duration/ Follow Up	Until disease progression unless the subject fulfilled one of the discontinuation criteria. A safety follow-up period lasted for 60 days after the last dose of epcoritamab. Survival status was assessed at least every 3 months after last administration of epcoritamab until the subject died or withdrew from the trial.
No. of patients enrolled	Dose Escalation Part: N=6 (48 mg full dose only). DLBCL Expansion Part: N=36 subjects with DLBCL FL Expansion Part: N=21 subjects with FL
Study Population	Subjects enrolled in both the Dose Escalation and Monotherapy Expansion Parts of the trial were of Asian race and Japanese ethnicity, had relapsed or refractory CD20+ mature B-cell neoplasm, and were previously treated with at least 2 lines of systemic antineoplastic therapy including at least 1 anti-CD20 mAb-containing therapy.
No. of Centers and Countries	Dose Escalation Part: 6 sites in Japan DLBCL Cohort, Monotherapy Expansion Part: 15 sites in Japan FL Cohort, Monotherapy Expansion Part: 12 sites in Japan

Abbreviations: ADA = anti-drug antibody; AE= adverse event; aNHL = aggressive B-cell non-Hodgkin lymphoma; C = cycle; CR = complete response; DLBCL = diffuse large B-cell lymphoma; DLT = dose limiting toxicity; DOCR = duration of complete response; DOR = duration of response; FL = follicular lymphoma; iNHL = indolent B-cell non-Hodgkin lymphoma; MRD = minimal residual disease; MZL = marginal zone lymphoma; PK = pharmacokinetics; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PR = partial response; RP2D = recommended phase 3 dose; SLL = small lymphocytic lymphoma; TTNT = time to next anti-lymphoma therapy; TTR = time to response.

The Applicant's Position:

The pivotal aNHL expansion cohort of the GCT3013-01 trial (N=157 subjects) provides the primary data analysis set supporting the assessment of the efficacy of epcoritamab in subjects with R/R LBCL. LBCL subtypes assessed in this cohort included 139 subjects with DLBCL, 9 subjects with HGBCL, 5 subjects with FL grade 3B, and 4 subjects with PMBCL. Among the subjects enrolled in the DLBCL cohort, 12 were found to have DH/TH lymphoma by central FISH analysis and, thus, can be classified as having HGBCL with MYC and BCL2 and/or BCL6 rearrangements using the most recent WHO 2016 criteria.

Key supportive efficacy data from Japanese subjects with R/R DLBCL in the Monotherapy Expansion Part of the GCT3013-04 trial (N=36; referred to as 04-DLBCL) were generally consistent with the results from the GCT3013-01 trial and are summarized in this application.

The evaluation of epcoritamab safety was based on data from 2 clinical trials: GCT3013-01 and GCT3013-04.

The primary safety analysis set for epcoritamab (N=167 subjects) was based on the pivotal GCT3013-01 trial, which provided the largest population of subjects with LBCL from a single trial. Data from the Dose Escalation and Expansion Parts were pooled for subjects who were assigned to receive the 48 mg full dose and received at least 1 dose of epcoritamab, resulting in an analysis set of 167 subjects with R/R LBCL. This analysis set includes 148 subjects with R/R DLBCL and 19 subjects with non-DLBCL subtypes. This group is referred to as the Safety Pool 01 LBCL group (N=167) and is the primary focus of this safety summary.

The supportive safety analysis set for epcoritamab (N=374 subjects) included all subjects with B-NHL subtypes from the pooled GCT3013-01 and GCT3013-04 trials and provided the largest pool of safety data. Data from the Dose Escalation and Expansion Parts of both trials were pooled for subjects who were assigned to receive the 48 mg full dose and received at least 1 dose of epcoritamab. In addition to data from 208 subjects with LBCL (167 from GCT3013-01 and 41 from GCT3013-04), data from 166 subjects with other B-NHL subtypes (128 subjects with iNHL and 38 subjects with MCL) was included. This group is referred to as the All B-NHL group (N=374) and allows assessments of safety in subjects with a diverse set of B-NHL subtypes.

The FDA's Assessment:

The FDA agrees with the Applicant's position that the pivotal aNHL expansion cohort of the GCT3013-01 trial (N=157 patients) provides the primary data analysis set supporting the assessment of the efficacy of epcoritamab in patients with R/R LBCL and the Monotherapy Expansion Part of the GCT3013-04 trial (N=36; referred to as 04-DLBCL) provides supportive efficacy data from Japanese patients with R/R DLBCL.

The FDA review of safety is primarily based on data from the 157 patients with R/R LBCL from the Expansion Part of Study GCT3013-01 who received the dose and schedule of epcoritamab intended for registration. This population was also used in the supportive safety population,

which consisted of 374 patients with either R/R LBCL, MCL, or indolent lymphoma (FL, MZL, SLL) who treated at the RP2D of epcoritamab on GCT3013-01 or GCT3013-04. All major safety analyses were based on a data cutoff of 31 January 2022 unless otherwise noted.

8 Statistical and Clinical Evaluation

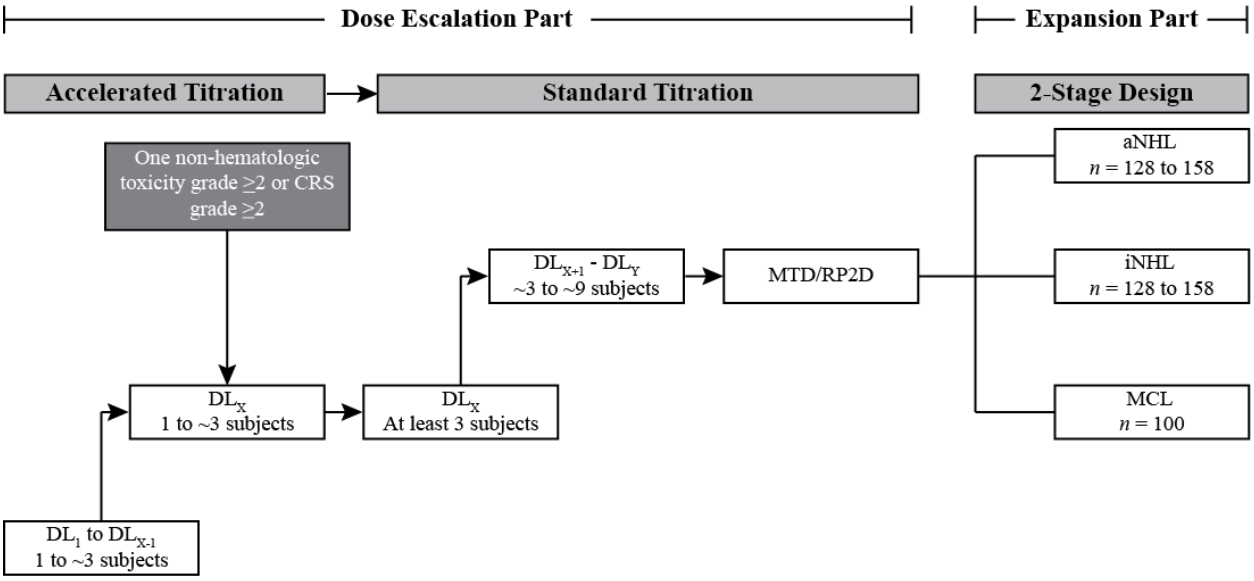
8.1.Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Pivotal aNHL Expansion Cohort of Trial GCT3013-01

Trial Design

The Applicant's Description:
Study Design
This is a first-in-human (FIH), open-label, phase 1/2, multicenter, dose escalation/expansion, multi-cohort, single arm trial in subjects 18 years or older who had relapsed, progressive and/or refractory mature B-cell lymphoma. The trial consists of 2 parts: a Dose Escalation Part and an Expansion Part. The trial design is illustrated in Figure 10.

Figure 10: Applicant – Overview of GCT3013-01 Trial Design



aNHL = aggressive non-Hodgkin lymphoma subtypes; CRS = cytokine release syndrome (according to (Lee et al., 2019)); DL = dose level; iNHL = indolent 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 epcoritamab recommended phase 2 dose (RP2D) regimen was selected based upon results from the Dose Escalation Part of the trial. In the Expansion Part of the trial, the epcoritamab RP2D was administered as monotherapy by subcutaneous (SC) injection as described in Section 6.2.2.1.

Trial Location
The aNHL cohort of the Expansion Part was conducted across 54 sites as described in Table 24.

The FDA's Assessment:
The FDA agrees with the Applicant's description of the study design. Study GCT3013-01 is an open-label, phase 1/2, multicenter, dose escalation/expansion, multi-cohort, single-arm trial in patients 18 years or older who had relapsed, progressive and/or refractory mature B-cell lymphoma. The trial consists of 2 parts: a Dose Escalation Part and an Expansion Part. The efficacy evaluation was based on the data from the expansion part.

Eligibility Criteria

The Applicant's Description:
Subjects enrolled in the aNHL expansion cohort were aged 18 years or older with an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1 or 2, and had documented evidence of CD20+ mature B-cell neoplasm. Subjects must have had measurable disease. Subjects must have had DLBCL (de novo or transformed from all indolent subtypes including Richter's transformation), including subjects with double-hit (DH) or triple-hit (TH) DLBCL (technically classified in WHO 2016 as HGBCL, with MYC and BCL2 and/or BCL6 rearrangements), or other aNHL subtypes (including PMBCL, HGBCL, or FL 3B). Subjects must have had relapsed or refractory disease and previously been treated with at least 2 lines of systemic antineoplastic therapy, including at least 1 anti CD20 mAb-containing therapy. Subjects also must have failed prior autologous hematopoietic stem cell transplantation (HSCT) or were ineligible for autologous HSCT due to age, ECOG performance status, comorbidities, and/or insufficient response to prior treatment. Subjects must have had lymphocyte counts <5 x 10^9/L.
Subjects were excluded from participating in any the expansion part of the trial if they had primary central nervous system (CNS) lymphoma or known CNS involvement, past or current malignancy (except for those noted in the protocol), aspartate transaminase (AST) or alanine transaminase (ALT) >3 × upper limit of normal (ULN), total bilirubin >1.5 × ULN, CrCl by Cockroft Gault <45 mL/min, clinically significant cardiac disease, chronic ongoing infectious diseases, diseases or treatments resulting in immunosuppression, or seizure disorders requiring therapy.

The FDA's Assessment:
The FDA agrees with the Applicant's description of the eligibility criteria.

Study Endpoints

The Applicant's Description:
Primary Endpoint

- Overall response rate (ORR) determined by Lugano criteria as assessed by Independent Review Committee (IRC).

Secondary Endpoints

- Duration of response (DOR), complete response (CR), duration of complete response (DOCR), progression-free survival (PFS), and time to response (TTR) determined by Lugano criteria as assessed by IRC.
- Overall survival (OS).
- Time to next (anti-lymphoma therapy) (TTNT).
- Rate of MRD negativity.
- Safety (ie, adverse events (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 and incidence of anti-drug antibodies (ADAs) to epcoritamab.
- Changes in lymphoma symptoms as measured by the Functional Assessment of Cancer Therapy - Lymphoma (FACT-Lym).

The FDA's Assessment:
The FDA agrees with the Applicant's description of the study primary endpoint and secondary endpoints.

Statistical Analysis Plan and Amendments

The Applicant's Description:
No formal hypothesis testing was performed on the aNHL expansion cohort. Analyses of trial participants and efficacy were performed using the Full Analysis Set (FAS), defined as all subjects who had received at least one dose of epcoritamab. Sensitivity analyses of efficacy were based on the per protocol (PP; all subjects in the FAS with measurable disease at baseline and no important protocol deviations), response evaluable set (RES; all subjects in the FAS with measurable disease at baseline, and either at least 1 postbaseline disease evaluation or had died within 60 days of first dose without postbaseline disease assessment), and modified response evaluable set (mRES; all subjects in the RES who had received at least 1 full dose of epcoritamab) analysis sets. Analysis of safety was performed using the Safety Analysis Set (SAF), which was identical to the FAS. Sensitivity analyses were performed using additional predefined analysis populations.

Sample Size

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

Efficacy and Safety

Unless otherwise specified, results will be summarized separately for subjects with DLBCL, other subtypes, and overall.

Response to study treatment drug and disease progression was centrally reviewed by an IRC, in addition to investigator evaluation. Efficacy analyses, including BOR, ORR, CR rate, DOR, TTR, and PFS were per Lugano criteria. Date of PD is defined as the earliest date of documented progression after which there is no more PR or CR assessment.

Safety analyses included exposure, dose delay/re-priming, subsequent anti-lymphoma therapies, and AEs.

Continuous data were summarized using descriptive statistics such as mean, standard deviation, median and range. Categorical data were summarized using frequency count as well 95% exact confidence interval (CI), if applicable. For time to event data, the Kaplan-Meier method was used for descriptive summaries.

Changes from Originally Planned Analysis

Forest plots were not produced for PFS or OS, as had originally been planned. Instead, results for the subgroup analysis of PFS and OS were presented in table format for this single-arm aNHL cohort.

Due to missing baseline tumor biopsies, subject consent preference, and/or unevaluable assay results, all exploratory MRD analyses were performed using the MRD-evaluable subset, which included subjects who had at least one baseline or on treatment MRD sample and were either MRD positive or not evaluated at baseline.

MRD tests were to be performed using PBMCs (from whole blood samples). However, exploratory analysis of MRD negativity was performed in plasma ctDNA samples due to inadequate sensitivity of the PBMC assay.

A retrospective, central FISH analysis was performed on available diagnostic baseline tumor tissue sections to identify HGBCL with MYC and BCL2 and/or BCL6 rearrangements (ie, DH/TH lymphomas) with a consistent method.

The FDA's Assessment:

The FDA agrees with Applicant's description of the Statistical Analysis Plan; no formal hypothesis testing was performed on the aNHL expansion cohort. The 35% ORR rate was considered as a benchmark based on therapies with regular approval or standard of care regimens to inform the proposed sample size. The FDA agrees with Applicant's calculation of sample size.

Protocol Amendments

The Applicant's Description:

A total of 7 protocol amendments were made to the original protocol Version 2.0 (dated 15 Nov 2017) as of the data cutoff date of 31 Jan 2022. The original protocol version 1.0 was dated 09 Nov 2017 but was not submitted. A summary of key changes with each protocol amendment is provided in Table 25. Protocol Amendments 1 through 4 were not applicable to the Expansion Part of this trial and are not included.

Table 25: Applicant – Protocol Amendments for GCT3013-01

Amendment Number and Version	Issue Date	Key Changes
Amendment 5; Version 7.0	4 Nov 2019	Amendment 5 was prepared to provide details regarding the Expansion Part of the trial. • Rationale, trial design, objectives/endpoints, inclusion/exclusion criteria, dose schedule and administration, statistical analysis (including sample size), safety and other relevant sections in the protocol were updated to include information for the Expansion Part. • Definition of end-of-trial was updated. • Clarified that, in the Dose Escalation Part of the trial, dose escalation could continue as planned with the Modified Bayesian optimal interval design if a 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 Number and Version	Issue Date	Key Changes
Amendment 6; Version 8.0	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 Expansion Part of the trial. • Inclusion and exclusion criteria were revised for the 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 hospitalization was only for 24 hours after the third dose (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 Expansion Part, a bone marrow biopsy was mandated at screening to assess bone marrow involvement. • Rationale for the R2PD to be used in the Expansion Part was added. • Qualitative interviews (patient-reported outcome assessment) were added to the PROs in the Expansion Part.
Amendment 7; Version 9.0	23 Sep 2020	A cohort of subjects with MCL was added to the Expansion Part of the trial. As a result, the trial design, inclusion/exclusion criteria, objectives and endpoints, statistical analysis and other relevant sections of the protocol were updated. Other key changes made to the protocol were: • Added 'Duration of CR (DOCR)' to the secondary endpoints to support the objective of: "To further evaluate clinical efficacy as determined by Lugano criteria.". • status by detection of cancer cell gene sequences' was changed to 'Rate of MRD negativity'. • Text was added to clarify that following trial termination (or completion), best effort was to be made by the sponsor to provide post-trial access to epcoritamab for those ongoing trial subjects with a potential treatment benefit. • Dose modification criteria for the Expansion Part were updated to incorporate findings from the ongoing trial. • Text was added to provide clarity on true progression versus pseudo-progression/tumor flare. • Added appendix for grading and management of ICANS.

Abbreviations: CR = complete response; DOCR = duration of complete response; eCRF = electronic case report form; ICANS = immune effector cell-associated neurotoxicity syndrome; IRC = Independent Review Committee;

MCL = mantle cell lymphoma; MRD = minimal residual disease; PRO = patient-reported outcome; RP2D = recommended phase 2 dose.

The FDA's Assessment:
The FDA agrees with the summary of Protocol Amendments for GCT3013-01. These amendments are not expected to have an appreciable impact on the efficacy assessment.

8.1.2. Study Results: Pivotal aNHL Expansion Cohort of Trial GCT3013-01

Compliance with Good Clinical Practices

Data:
Investigator sites and service provider audits were conducted to assess compliance with Good Clinical Practice (GCP). Site audits were conducted undertaking a risk-based approach. Five sites were audited during the expansion part of the trial at the time of the data cutoff. In addition, several vendors were audited. A consolidated audit certificate is provided in Appendix 16.1.8 of the CSR.

The Applicant's Position:
The trial was conducted in accordance with the protocol and the amendments, the ICH E6 (R2) guideline for GCP, applicable local regulations, and ethical principles that have their origins in the Declaration of Helsinki. In addition, the trial was conducted in accordance with US FDA 21 Code of Federal Regulations parts 312, 50, and 56, and the directive 2001/20/EC of the European Parliament.

The FDA's Assessment:
The FDA agrees with the Applicant's summary of compliance with good clinical practice.

Financial Disclosure

Data:
Genmab and AbbVie checked all 58 clinical sites that enrolled at least 1 subject in the aNHL cohort of Study GCT3013-01, as well as the IRC members. Three investigators were identified to have financial payments above $25,000.

The Applicant's Position:
It is unlikely that the payments biased the study results based on the following:

- Primary efficacy analysis was performed by IRC
- In total 58 sites enrolled, among which 54 sites treated 157 subjects. The sites, at which these 3 investigators participated, together treated 4 subjects.
- Diligent monitoring, as frequent as permitted during the COVID pandemic, of clinical trial

sites were conducted
- Validity of the data was confirmed by standard monitoring procedures

The FDA's Assessment:
The FDA agrees with the Applicant's summary of financial disclosures and the Applicant's position. See Section 19.2 for additional information.

Patient Disposition

Data:
Subject disposition is provided in Table 26 for the aNHL Expansion Cohort.

Table 26: Applicant – Disposition of Subjects – GCT3013-01 aNHL Cohort, Expansion Part (Full Analysis Set)

Number of Treated Subjects, n (%)	aNHL Cohort		
	DLBCL (N=139)	Other Subtypes[a] (N=18)	LBCL (N=157)
Ongoing trial treatment	47 (33.8%)	4 (22.2%)	51 (32.5%)
Discontinued trial treatment	92 (66.2%)	14 (77.8%)	106 (67.5%)
Primary reason for treatment discontinuation			
Progressive disease[b]	72 (51.8%)	11 (61.1%)	83 (52.9%)
Clinical progression	12 (8.6%)	2 (11.1%)	14 (8.9%)
Disease progression according to response criteria	60 (43.2%)	9 (50.0%)	69 (43.9%)
Adverse event	11 (7.9%)	0	11 (7.0%)
Death	0	0	0
Withdrawal by subject	3 (2.2%)	1 (5.6%)	4 (2.5%)
Decision to proceed with transplant	5 (3.6%)	2 (11.1%)	7 (4.5%)
Other[c]	1 (0.7%)	0	1 (0.6%)
Subjects remain on trial	76 (54.7%)	12 (66.7%)	88 (56.1%)
Discontinued from trial	63 (45.3%)	6 (33.3%)	69 (43.9%)
Death	53 (38.1%)	5 (27.8%)	58 (36.9%)
Lost to follow up	1 (0.7%)	0	1 (0.6%)
Subject withdrew consent from trial	9 (6.5%)	1 (5.6%)	10 (6.4%)

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

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

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

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

Data cutoff date: 31 Jan 2022

Source: GCT3013-01-EXP-aNHL CSR Table 14.1.1.1.1 and Listing 16.2.3.1.

The Applicant's Position:

As of the data cutoff date of 31 Jan 2022, 106 (67.5%) subjects with LBCL had discontinued epcoritamab treatment and 51 (32.5%) subjects with LBCL were continuing on epcoritamab treatment.

The most frequent reason for treatment discontinuation was disease progression in 83 (52.9%) subjects. AEs leading to treatment discontinuation were reported in 11 (7.0%) subjects.

A total of 69 (43.9%) subjects with LBCL permanently discontinued the trial. The most common reason for trial discontinuation was death (58 [36.9%] subjects).

The FDA's Assessment:

The FDA agrees with the Applicant's position. As shown in Table 27, 51 patients remained on active treatment by the data cutoff. For the remaining 106 patients, the major reason for treatment discontinuation was progressive disease, accounting for 53% (83/157) of patients. Although 68% of patients discontinued treatment, 44% (69/157) discontinued the trial, mostly due to death, which occurred in 37% (58/157) of patients.

Table 27: FDA Summary of Patient Disposition in Primary Efficacy Population from GCT3013-01

		Primary Efficacy Population N = 157
Median duration of study follow-up, months (range)		10.7 (0.3-17.9)
Treatment Status, n (%)		
Treatment ongoing		51 (32)
Treatment discontinued		106 (68)
Treatment Discontinuation Reason	Progressive Disease	83 (53)
	Adverse Event	11 (7)
	Transplant	7 (5)
	Patient decision	4 (3)
	Other[a]	1 (0.6)
Trial Status, n (%)		
Remain on trial		88 (56)
Discontinued trial		69 (44)
Trial Discontinuation Reason	Death	58 (37)
	Lost to Follow-up	1 (0.6)
	Patient withdrawal	10 (6)

[a] Bridging therapy for CAR T-cell therapy
Source: FDA analysis, data cutoff 31 Jan 2022

Protocol Violations/Deviations

Data:
At least one important protocol deviation occurred in 6 (3.8%) subjects in the aNHL expansion cohort. Important protocol deviations included the following:

- Enrollment criteria (3 subjects):
  - subject did not meet inclusion criteria criterion No. #6, local laboratories pre-C1D1 platelet level was 47×10^9/L, under the required level of 50×10^9/L
  - subject did not meet inclusion criterion criteria No. #7, local laboratories pre-C1D1 neutrophil level was 0.5×10^9/L, under the required level of $\geq 1.0 \times 10^9$
  - complete response for clear cell renal cell carcinoma was maintained <2 years prior to first dose, a violation of exclusion criterion criteria No. #21 in the Expansion Part of the trial; subject had received prior allogeneic HSCT
- Dosing (2 subjects):
  - prophylactic medication administered 3 days instead of 4 days for C1D1
  - mandatory prophylactic corticosteroids were not administered at C1D17
- Informed consent (1 subject):
  - subject was incorrectly consented to the wrong trial (a different trial with epcoritamab being conducted at the same site); however, the correct informed consent form was signed prior to trial drug administration

The Applicant's Position:
None of the important protocol deviations were deemed to have had a meaningful impact on the interpretation of the trial results.

The FDA's Assessment:
The FDA agrees with the Applicant's position.

Table of Demographic Characteristics

Data:
A summary of demographic characteristics in the aNHL Expansion Cohort is provided in Table 28.

Table 28: Applicant – Demographic Characteristics – GCT3013-01 aNHL Cohort, Expansion Part (Full Analysis Set)

Demographic Parameters	aNHL Cohort		
	DLBCL	Other Subtypes[a]	LBCL

	(N=139)	(N=18)	(N=157)
Sex			
Male	85 (61.2%)	9 (50.0%)	94 (59.9%)
Female	54 (38.8%)	9 (50.0%)	63 (40.1%)
Age, years			
Mean (SD)	63.7 (12.63)	50.9 (16.40)	62.3 (13.68)
Median	66.0	55.5	64.0
Min, max	22, 83	20, 74	20, 83
Age category, years			
<65 years	66 (47.5%)	14 (77.8%)	80 (51.0%)
65 to <75 years	44 (31.7%)	4 (22.2%)	48 (30.6%)
≥75 years	29 (20.9%)	0	29 (18.5%)
Race			
White	84 (60.4%)	12 (66.7%)	96 (61.1%)
Asian	27 (19.4%)	3 (16.7%)	30 (19.1%)
Other	5 (3.6%)	2 (11.1%)	7 (4.5%)
Not Reported[b]	23 (16.5%)	1 (5.6%)	24 (15.3%)
Ethnicity			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	21 (15.1%)	3 (16.7%)	24 (15.3%)

Abbreviations: aNHL = aggressive B-cell non-Hodgkin lymphoma; DLBCL = diffuse large B-cell lymphoma; LBCL = large B-cell lymphoma; SD = standard deviation.

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

[b] Not reported in non-US countries

Data cutoff date: 31 Jan 2022

Source: GCT3013-01-EXT-aNHL CSR Table 14.1.1.2

The Applicant's Position:

The aNHL expansion cohort included elderly subjects (approximately 50% of subjects were ≥65 years of age) with LBCL. Of the subjects with race information available, 96 (61.1%) were white and 30 (19.1%) were Asian.

The FDA's Assessment:

The FDA analysis of the demographic characteristics for the 157 patients included in the primary efficacy analysis is summarized in Table 29. The FDA agrees with the Applicant's summary as it pertains to these 157 patients. Although the median age was 64 years of age, the population did have 18% of patients 75 years or older. The majority were Male (60%), White (61%), non-Hispanic (15%), and were enrolled outside of the U.S (85%). Besides the presence of 30 Asian patients, who accounted for 19% of the population, there was limited representation of other racial or ethnic groups. No Black or African American patients and Hispanic or Latino patients were noted, limiting assessment of the effect of epcoritamab in these minority populations. Notably, a large number of patients did not report race (15%) or ethnicity (85%), which may have resulted in underestimation of some subgroups.

Table 29: FDA Summary of Patient Demographics in Primary Efficacy Population in GCT3013-01

Characteristic	Primary Safety Population N = 157
Age	
Median	64
Range	(20, 83)
≥65 to <75, n (%)	48 (31)
≥75, n (%)	29 (18)
Sex, n (%)	
Male	94 (60)
Female	63 (40)
Race, n (%)	
White	96 (61)
Black	0
Asian	30 (19)
Native Hawaiian or Pacific Islander	1 (0.6)
American Indian or Alaska Native	0
Other	6 (4)
Not Reported	24 (15)
Ethnicity, n (%)	
Hispanic	0
Non-Hispanic	24 (15)
Not reported	133 (85)
Country, n (%)	
US	24 (15)
Non-US	133 (85)
Australia	22 (14)
Canada	1 (0.6)
Denmark	10 (6)
France	23 (15)
Germany	5 (3)
Italy	3 (2)
Japan	0
Korea	21 (13)
Netherlands	14 (9)
Poland	6 (4)
Singapore	6 (4)
Spain	10 (6)
Sweden	0

Characteristic	Primary Safety Population N = 157
United Kingdom	12 (8)
ECOG PS, n (%)	
0	74 (47)
1	78 (50)
2	5 (3)

Abbreviations: US, United States; ECOG PS Eastern Cooperative Oncology Group Performance Status
Source: FDA Analysis

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Data:
Baseline disease characteristics in the aNHL Expansion Cohort are summarized in Table 30. Prior anticancer therapies are summarized in Table 31.

Table 30: Applicant – Key Baseline Disease Characteristics – GCT3013-01 aNHL Cohort, Expansion Part (Full Analysis Set)

Number of treated subjects, n (%)	aNHL Cohort		
	DLBCL (N=139)	Other Subtypes[a] (N=18)	LBCL (N=157)
Disease type at trial entry			
DLBCL	139 (100%)	0	139 (88.5%)
HGBCL	0	9 (50.0%)	9 (5.7%)
PMBCL	0	4 (22.2%)	4 (2.5%)
FL grade 3B	0	5 (27.8%)	5 (3.2%)
DLBCL type			
De novo	97 (69.8%)	-	97 (61.8%)
Transformed	40 (28.8%)	-	40 (25.5%)
Disease type at initial diagnosis			
FL	32 (23.0%)	-	32 (20.4%)
MZL	4 (2.9%)	-	4 (2.5%)
SLL	1 (0.7%)	-	1 (0.6%)
Other	3 (2.2%)	-	3 (1.9%)
Unknown	2 (1.4%)	-	2 (1.3%)
Not applicable	0	18 (100%)	18 (11.5%)
DLBCL cell-of-origin classification per local laboratory[b]			
GCB	65 (46.8%)	0	65 (41.4%)
ABC/non-GCB	56 (40.3%)	0	56 (35.7%)

Number of treated subjects, n (%)	aNHL Cohort		
	DLBCL (N=139)	Other Subtypes[a] (N=18)	LBCL (N=157)
Unknown	18 (12.9%)	0	18 (11.5%)
Not applicable	0	18 (100%)	18 (11.5%)
Median time from initial diagnosis to first dose[c] (min, max), yrs	1.6 (0.0, 28.4)	1.9 (0.4, 8.2)	1.6 (0.0, 28.4)
MYC and BCL2 and/or BCL6 rearrangements per local laboratory			
Number evaluated	36	2	38
Double-hit lymphoma	10	1	11
Triple-hit lymphoma	6	0	6
Other	20	1	21
MYC and BCL2 and/or BCL6 rearrangements per central laboratory FISH analysis			
Number evaluated	88	11	99
Double-hit lymphoma	11 (12.5%)	1 (9.1%)	12 (12.1%)
Triple-hit lymphoma	1 (1.1%)	0	1 (1.0%)
Other	76 (86.4%)	10 (90.9%)	86 (86.9%)
Ann Arbor stage at Screening			
I	4 (2.9%)	1 (5.6%)	5 (3.2%)
IE	1 (0.7%)	0	1 (0.6%)
II	24 (17.3%)	3 (16.7%)	27 (17.2%)
IIE	6 (4.3%)	0	6 (3.8%)
III	16 (11.5%)	3 (16.7%)	19 (12.1%)
IIIE	1 (0.7%)	0	1 (0.6%)
IIIS	1 (0.7%)	0	1 (0.6%)
IV	86 (61.9%)	11 (61.1%)	97 (61.8%)
IPI (at study entry)			
0-2	55 (39.6%)	0	55 (35.0%)
≥3	82 (59.0%)	0	82 (52.2%)
Unknown	2 (1.4%)	0	2 (1.3%)
Not applicable	0	18 (100%)	18 (11.5%)
Presence of constitutional symptoms	20 (14.4%)	3 (16.7%)	23 (14.6%)
Night sweats	12 (8.6%)	2 (11.1%)	14 (8.9%)
Weight loss (>10% over last 6 months)	4 (2.9%)	0	4 (2.5%)
Fever	6 (4.3%)	1 (5.6%)	7 (4.5%)
Extreme fatigue	6 (4.3%)	0	6 (3.8%)

Abbreviations: ABC = activated B-Cell; DLBCL = diffuse large B-cell lymphoma; FL = follicular lymphoma; GCB = germinal center B-cell; HGBCL = high-grade B-cell lymphoma; IHC = immunohistochemistry; IPI = International Prognostic Index; LBCL = large B-cell lymphoma; MZL = marginal zone lymphoma; NA = not applicable; PMBCL = primary mediastinal large B-cell lymphoma; SLL = small lymphocytic lymphoma.

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

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

[c] Time from diagnosis of disease recorded at time of trial entry
Data cutoff date: 31 Jan 2022
Source: GCT3013-01-EXP-aNHL CSR Table 14.1.1.3 and Table 4.1.1.3.1.

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Table 31: Prior Anticancer Therapies – GCT3013-01 aNHL Cohort, Expansion Part (Full Analysis Set)

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

Abbreviations: aNHL = aggressive B-cell non-Hodgkin lymphoma; ASCT = autologous stem cell transplantation; CAR T = chimeric antigen receptor T-cells; DLBCL= diffuse large B-cell lymphoma; FL= follicular lymphoma; LBCL = large B-cell lymphoma.

[a] Other includes 9 subjects with high-grade B-cell lymphoma (HGBCL), 5 subjects with follicular lymphoma (FL) grade 3B and 4 subjects with primary mediastinal B-cell lymphoma (PMBCL).
[b] Subject was considered primary refractory if the subject is refractory to frontline anti-lymphoma therapy.
[c] Subject was considered refractory if the subject experienced disease progression or stable disease as best response or disease progression within 6 months after therapy completion.
[d] Subject was considered relapsed if the subject experienced disease progression >6 months after last treatment.
Data cutoff date: 31 Jan 2022
Source: GCT3013-01-EXP-aNHL CSR Table 14.1.1.6.1

The Applicant's Position:

The population included in the aNHL Expansion Cohort reflects a broad and representative population of R/R LBCL patients. This trial allowed for inclusion of heavily pre-treated and highly refractory subjects, including those who were ineligible for ASCT, previous recipients of CAR T therapy, and subjects who had disease transformed from indolent lymphomas. The trial included subjects who had tumors with high-risk characteristics, including high-grade B cell lymphoma, transformed disease, and disease refractory to first-line therapy, refractory to most recent therapy, and/or refractory to all prior lines of therapy. This population presents treatment challenges, given historically poor responses and survival outcomes, as well as comorbid conditions and toxicities from prior therapies that impact treatment tolerability.

The FDA's Assessment:

The FDA analysis of the baseline disease and prior treatment characteristics of the primary efficacy population is shown in Table 32.

General disease and prior therapy assessment:

The FDA agrees with the Applicant's position in terms of the inclusion of a heavily pre-treated and highly refractory patient population, including a substantial number of patients with prior CAR T-cell therapy (39%) and autologous stem cell transplant (20%). At screening, the majority of patients had DLBCL (89%) and advanced stage disease (75%, Stage III or IV).

Table 32: FDA Summary of Patient Baseline Disease and Prior Treatment Characteristics in the Primary Efficacy Population in GCT3013-01

Disease Characteristic		Primary Safety Population N = 157
Diagnosis[a] n (%)	DLBCL	139 (89)
	De novo	99 (63)
	Transformed	40 (25)
	FL Grade 3B	5 (3)
	HGBCL	9 (6)
	PMBCL	4 (3)

Disease Characteristic		Primary Safety Population N = 157
Stage n (%)	I	6 (4)
	II	33 (21)
	III	21 (13)
	IV	97 (62)
Prior Lines of Therapy	Median	3
	Range	2-11
	1, n (%)	0
	2, n (%)	46 (29)
	3, n (%)	50 (32)
	≥4, n (%)	61 (39)
Primary refractory disease		96 (61)
Prior therapy	Anti-CD20± alkylating agent	157 (100)
	Anthracyclines	154 (98)
	Anti-CD19	7 (4)
	Polatuzumab	17 (11)
	CAR-T	61 (39)
	ASCT	31 (20)

Abbreviations: DLBCL, diffuse large B cell lymphoma; high-grade B-cell lymphoma; PMBCL, primary mediastinal B-cell lymphoma; FL, follicular lymphoma; ASCT, autologous stem cell transplant; CAR-T, chimeric antigen T cell therapy
[a] Diagnosis provided at entry prior to subset of 88 patients with DLBCL further tested by FISH
Source: FDA Analysis

LBCL subtypes and Indication:

Although the entire population of 157 patients with LBCL is used for the FDA efficacy analysis, the exact breakdown by subtype is of importance, especially in support of the indicated population. The FDA did not agree with the Applicant that there was sufficient representation of multiple other subtypes of R/R LBCL to justify extension of the indication to all R/R LBCL. The initial breakdown shown in Table 32 was based on report at entry and demonstrated few patients with HGBCL (6%; 9/157), FL Grade 3B (3%; 5/157), or PMBCL (3%, 4/157). However, following reassessment of 88 patient samples by central laboratory FISH analysis for *MYC*, *BCL2*, and/or *BCL6* rearrangements, 12 patients initially diagnosed as having DLBCL were reclassified as having HGBCL. Thus, as shown in Table 33, the final population contained 13% HGBCL rather than 6% and 81% DLBCL instead of 89%. Based on this reclassification, the final population supports an adequate evaluation in DLBCL NOS, DLBCL transformed from indolent lymphoma, and HGBCL.

Table 33: FDA Summary of Reclassification of DLBCL and HGBCL based on FISH Analysis

Diagnosis	Primary Safety Population N = 157 n, (%)
Diagnosis before FISH analysis	
DLBCL	139 (89)
HGBCL	9 (6)
Diagnosis after FISH analysis	
DLBCL	127 (81)
HGBCL	21 (13)
Source: FDA Analysis	

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Data:

Treatment Compliance:

The median relative dose intensity for subjects in the aNHL Expansion Cohort was 100% (range: 50%, 104%) in C1 to C3 (QW dosing), 100% (range: 77%, 102%) in C4 to C9 (Q2W dosing), and 100% (range: 80%, 103%) C10+ (Q4W dosing). For C1 to C3, RDI was ≥90% for 127 (86.4%) subjects; for C4 to C9 and C10+ RDI was ≥90% for more than 95% of participants.

Overall, 62 (39.5%) subjects with LBCL required at least one dose delay during the trial, including 46 (29.3%) subjects who required a dose delay due to an AE and 20 (12.7%) subjects who required a dose delay for another reason, including COVID-19 control measures. No subjects required epcoritamab repriming due to a dose delay. Dose reductions were not allowed in this trial.

Concomitant Medications:

Common (≥20%) concomitant medications included paracetamol in 107 (68,2%) subjects, sulfamethoxazole-trimethoprim in 98 (62.4%) subjects, allopurinol in 71 (45.2%) subjects, acyclovir in 64 (40.8%) subjects, valacyclovir in 46 (29.3%) subjects, sodium chloride in 42 (26.8%) subjects, pantoprazole in 38 (24.2% subjects), and dexamethasone and omeprazole in 34 (21.7%) subjects each.

All 157 subjects in the aNHL Expansion Cohort received mandatory corticosteroids pre- and post epcoritamab administration per protocol. The use of corticosteroids, anti-cytokine therapy, or other supportive therapies for the treatment of CRS or ICANS is summarized in Section 8.2.5.

Rescue Medication Use:

There are no reversal agents for epcoritamab.

The Applicant's Position:

Subjects' compliance to study drug allowed adequate assessment of safety and efficacy of

subjects in this trial population.

The FDA's Assessment:
The FDA agrees with the Applicant's position. The FDA notes that prophylaxis against *Pneumocystis jirovecii* and against herpes virus infection was mandatory under certain circumstances. However, in both cases, the compliance was below 100%.

Pneumocystis jirovecii Prophylaxis
Prophylaxis with oral trimethoprim/sulfamethoxazole was mandatory for the following scenarios:

a. When 4 or more consecutive days of corticosteroids are given OR
b. For patients who are considered at increased risk, e.g., patients with low CD4+ cell counts (<350 cell/µl)

Despite the fact that scenario "a" would occur in all patients during cycle 1 due to premedication requirements, only 59% of patients had an agent used for PJP prophylaxis accounted for at any point in cycle 1. Given that all patients would have met criteria and the potential serious risk of PJP, the USPI will recommend that PJP prophylaxis be provided prior to starting treatment with epcoritamab.

Herpes Virus Prophylaxis:
Prophylactic antiviral therapy (e.g., acyclovir 400 mg three times a day orally) is mandatory for a patient meeting the following criteria:

a. History of recurrent herpes virus infections
b. Herpes infection during previous anti-lymphoma therapy
c. Neutropenia and/or low CD4+ cell counts (<200 cells/µl)

The FDA analysis found that 68% of patients at any point had an antiviral prophylactic medication accounted as a concomitant medication and 64% of patients had one at the start or during Cycle 1. However, it is unclear how many patients in the trial met criteria for mandatory antiviral prophylaxis. Based on this analysis and uncertainty, the USPI will recommend consideration of initiating prophylaxis against herpes virus prior to starting therapy with epcoritamab to prevent herpes zoster reactivation.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

Data:
The primary efficacy endpoint for the aNHL Expansion Part of the GCT3013-01 trial is ORR as assessed by IRC using Lugano criteria is provided in Table 34.

Table 34: Applicant – Overall Response Rates Based on IRC Assessment Using Lugano Criteria – GCT3013-01 Expansion Part (Full Analysis Set)

	GCT3013-01 Expansion Part aNHL Cohort		
	DLBCL (N=139)	**Other Subtypes[a] (N=18)**	**LBCL (N=157)**
Overall response rate (ORR)[b] (95% CI)[c]	**86 (61.9%)** (53.3, 70.0)	**13 (72.2%)** (46.5, 90.3)	**99 (63.1%)** (55.0, 70.6)
Best overall response			
Complete response (CR)	54 (38.8%)	7 (38.9%)	61 (38.9%)
Partial response (PR)	32 (23.0%)	6 (33.3%)	38 (24.2%)
Stable disease (SD)	4 (2.9%)	1 (5.6%)	5 (3.2%)
Progressive disease (PD)	33 (23.7%)	4 (22.2%)	37 (23.6%)
Not evaluable (NE)	16 (11.5%)	0	16 (10.2%)

Abbreviations: aNHL = aggressive B-cell non-Hodgkin lymphoma; CI = confidence interval; DLBCL = diffuse large B-cell lymphoma; FL = follicular lymphoma; HGBCL = high-grade B-cell lymphoma; LBCL = large B-cell lymphoma; PMBCL = primary mediastinal large B-cell lymphoma.

[a] Other subtypes include 9 subjects with HGBCL, 5 subjects with FL grade 3B, and 4 subjects with PMBCL.

[b] Defined as CR+PR. Includes 10 subjects who had a PR or CR after initial assessment of PD or indeterminate response.

[c] Based on the Clopper and Pearson method.

Data cutoff date: 31 Jan 2022

Source: GCT3013-01-EXP-aNHLCSR Table 14.2.1.1.1

Sensitivity Analyses:

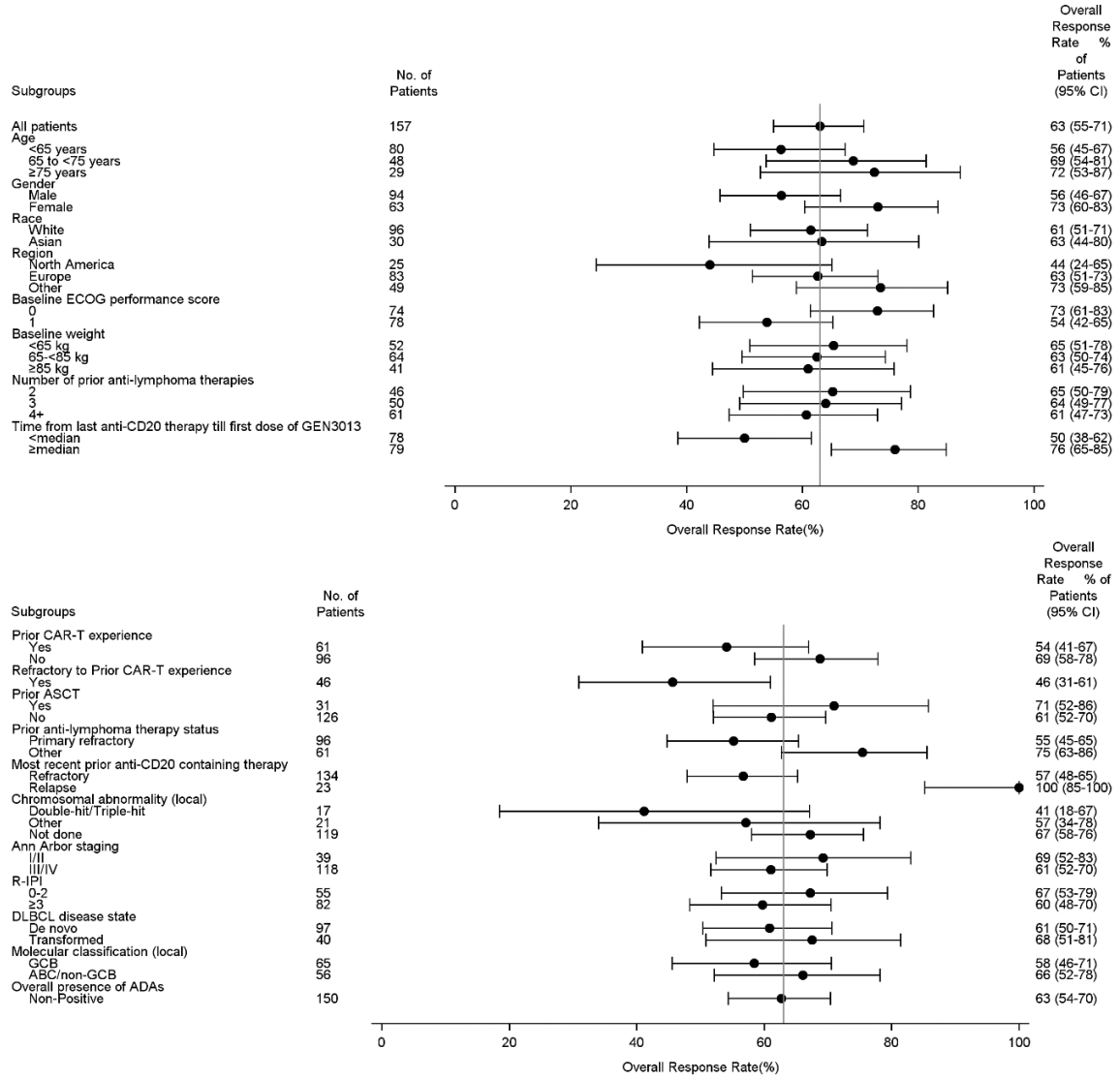
Response assessments were also conducted by the investigator as a supplementary analysis to the primary endpoint. The ORR (PR + CR) as assessed by the investigator was clinically meaningful at 58.6% (95% CI: 50.5, 66.4) in subjects with LBCL. The concordance rate for the primary efficacy endpoint between response assessments per IRC and per investigator was 88.9%.

Sensitivity analyses of ORR per IRC or investigator assessment in the PP, RES, and mRES populations were consistent, further supporting the robustness of the response results.

Subgroups:

Forest plots of ORR as assessed by IRC using Lugano criteria for prespecified subgroups of subjects with LBCL in the GCT3013-01 aNHL expansion cohort are shown in Figure 11.

Figure 11: Applicant – Forest Plot of ORR in Prespecified Subgroups of Subjects with LBCL as Assessed by IRC Using Lugano Criteria – aNHL Expansion Cohort (Full Analysis Set)



Abbreviations: ADA = antidrug antibody; aNHL = aggressive B-cell non-Hodgkin lymphoma; ASCT = autologous stem cell transplant; CAR T = chimeric antigen receptor T-cell; CI = confidence interval; DLBCL= diffuse large B-cell lymphoma; ECOG = Eastern Cooperative Oncology Group; GCB = germinal center B-cell; IHC = immunohistochemistry; No. = number; NR = not reached; ORR = overall response rate; R-IPI = revised international prognostic index.
Note: Subjects with molecular subtype of non-GCB per IHC and ABC per GEP are included in the non-GCB group.
Data cutoff date: 31 Jan 2022
Source: GCT3013-01-EXP-aNHL CSR Figure 14.2.1.1.2

The Applicant's Position:

Overall, epcoritamab induced deep responses across a broad population of difficult to treat subjects with R/R LBCL.

For almost all subgroups, results did not markedly differ from the ORR (63%; 95% CI: 55, 71) of the overall LBCL population (N=157), indicating that the benefit of epcoritamab was generally consistent and robust across prespecified subgroups examined, including subpopulations of LBCL that are traditionally difficult to treat, including subjects ≥75 years of age and those with prior CAR-T experience. This further supports the consistency of the benefit of epcoritamab therapy demonstrated in the GCT3013 01 aNHL expansion cohort.

The FDA's Assessment:

Assessment of Primary Endpoint and Sensitivity Analyses:

The FDA agrees with the Applicant's analysis results of ORR and best overall response rate in the prespecified subgroups of patients with LBCL as assessed by IRC using Lugano criteria. The reviewer was able to verify these analyses. Among the 157 patients, the ORR per IRC was 63% (95% CI: 55, 71), with 39% achieving best response of CR (95% CI: 31, 47).

The FDA also agrees with the Applicant's subgroups analysis results presented in the figure above, which demonstrated consistence in general across most prespecified subgroups. However, there were ORR variations in some subgroups, for example, for the prior anti-lymphoma therapy status, the ORR for the primary refractory category was 55% (95% CI: 45-65%) and the ORR for other category was 75% (95% CI: 63-88%).

Of note, FDA considers the statement "Overall, epcoritamab induced deep responses across a broad population of difficult to treat patients with R/R LBCL" to be misleading. FDA notes that there are no formal scientific definitions of "deep", "broad", or "difficult to treat". Furthermore, FDA notes that the number of patients in the analysis set with LBCL other than DLBCL is low relative to the overall LBCL population (18 out of 157 patients).

Even though these subgroups were pre-specified in the SAP, this pre-specification was as supportive analyses. That is, the Expansion Part was not specifically powered for any of these subgroups. Therefore, these subgroup analyses are considered to be exploratory only.

Assessment of Flare Reaction (Pseudoprogression) Events and Response

The association of epcoritamab with flare reaction is unknown. However, given the mechanism of action of epcoritamab, which results in stimulation of the immune system, there is potential for flare reaction. Thus, early imaging to assess response may detect increases in lesion size that may not be true progression. Interpretation of such imaging using the Lugano 2014 criteria may result in a designation of progressive disease and early termination of treatment. In Study

GCT3013-01, the primary endpoint is best response as assessed by IRC based on Lugano 2014 criteria. The protocol accounts for the potential for flare reaction or delayed response and requires that responses be assessed by IRC and investigator according to both the Lugano 2014 and the LYRIC criteria. Per protocol, the Sponsor is informed immediately following a patient's first progressive disease (PD) designation per Lugano 2014 and the Sponsor's Responsible Medical Officer (RMO) or delegate then confirms whether a true PD by both Lugano and LYRIC has occurred. If a true PD has not been met and, if clinically acceptable, the patient may continue trial treatment.

Based on this procedure, potential flare reaction was observed in 6% of patients (10/157) in the primary efficacy population (Table 35). All 10 patients had a potential progression assessed by the IRC documented at the first assessment on Week 6 as either an indeterminate response per LYRIC or PD (1 case SD) by Lugano criteria. A similar or more favorable response was assessed by the investigator at that same time point. All cases had a response of PR or CR demonstrated by Week 36 with most having a response either by the next scheduled assessment at week 12 or by the following assessment around week 18.

The Agency considered several factors when reviewing this data and determining whether these above patients should be considered as responders.

- The Lugano criteria include measures to account for tumor flare.
- GCT3013-01 specified assessment of the primary endpoint of best overall response according to Lugano criteria.
- GCT3013-01 was a single-arm trial based primarily on response and did not rely on time to event endpoints, in particular PFS, for which the occurrence of flare reactions and subsequent treatment decisions may introduce bias.
- GCT3013-01 prespecified an approach to account for early flare reaction, which was consistently applied and included assessment by IRC.

Based on the available data and the factors above, the Agency agreed with inclusion of these patients as responders.

The observation noted above suggest that flare reaction is a low-level occurrence in patients with LBCL treated with epcoritamab. These findings may suggest that if a potential flare reaction does occur, it will occur early (i.e., within 6 weeks) and be followed by a response in most cases. However, given that this observation is based on few patients, further studies evaluating epcoritamab in this patient population are warranted to continue to evaluate such a trend and to determine the potential impact, if any, on treatment management.

Table 35: FDA Summary of Potential Pseudoprogression Events

Patient	Pseudoprogression Event			1st Documented Response by IRC (*After* Pseudoprogression event)	Best Overall Response	
	Timing of Assessment	IRC	INV		IRC	INV
Based on LYRIC						
(b) (6)	Week 6	IR2	IR 2/3	Week 12, CR	CR	CR
	Week 6	IR1	IR 2/3	Week 36, PR	PR	PR
	Week 6	IR2	PR	Week 18, PR	CR	CR
	Week 6	IR3	SD	Week 17, PR	PR	SD
	Week 6	IR1	SD	Week 12, PR	PR	PR
Based on Lugano						
(b) (6)	Week 6	PD	CR	Week 12, CR	CR	CR
	Week 6	PD	PR	Week 12, CR	CR	CR
	Week 6	PD	PR	Week 12, PR	PR	PR
	Week 6	PD	SD	Week 9, PR	PR	SD
	Week 6	SD	PR	Week 12, CR	CR	CR

Abbreviations: LYRIC, lymphoma response to immunomodulatory therapy criteria; IRC, independent review committee; INV, investigator; IR, indeterminate response (based on LYRIC); CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease
Source: FDA adaptation of information contained in GCT3013-01 aNHL Expansion CSR

Data Quality and Integrity

Data:
N/A

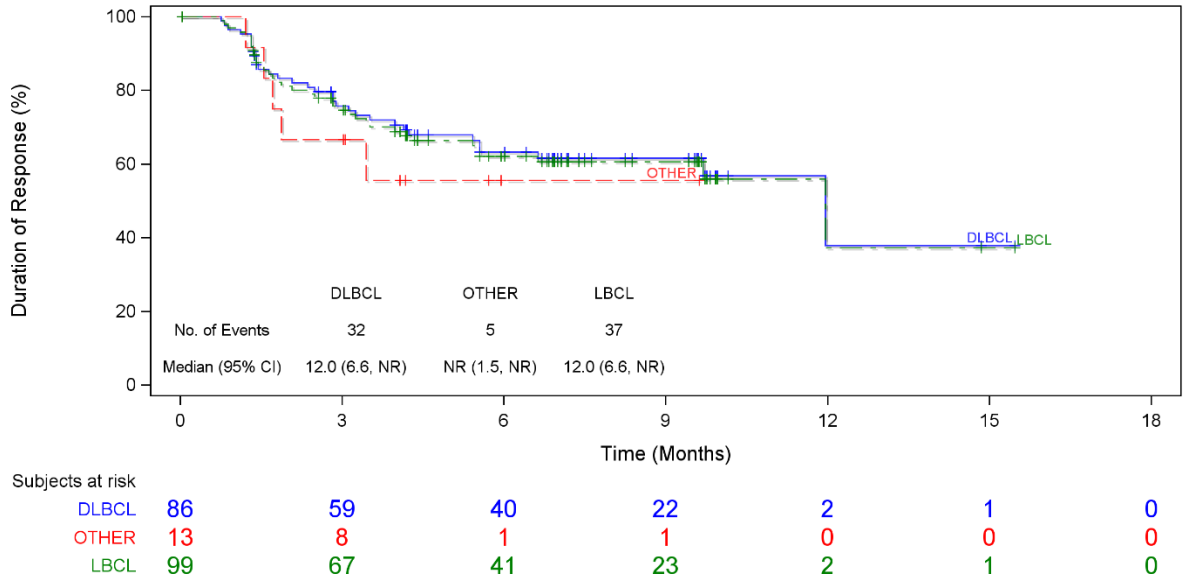
The Applicant's Position:
This trial was conducted in compliance with ICH GCP E6 (R2), and applicable regulatory requirements. Steps taken to ensure the accuracy and reliability of data included the selection of qualified investigators and appropriate trial sites, review of protocol procedures with the investigator and trial site personnel before the trial, periodic monitoring visits by the sponsor, and direct transmission of data from vendors into the sponsor's data base. Written instructions were provided for collection, handling, storage, and shipment of samples.
Clinical research associates conducted site visits to the investigational facilities for the purpose of monitoring various aspects of the trial. Instructions for data entry and completion were provided in the eCRF completion guidelines.
The sites had to complete the eCRFs in a timely manner and on an ongoing basis to allow regular review by the trial monitor. Instructions were provided in the eCRF completion

guidelines. Data entry was monitored by the CRO on an ongoing basis, and when delays were observed at sites for data entry, issues were escalated to the sponsor and mitigation plans were put in place to collect required data. During the trial, the COVID-19 pandemic significantly impacted the possibility of on-site monitoring in the majority of countries. Using a risk-based approach, reduced sourced data review was implemented and on-site monitoring and central monitoring focused on critical data /processes essential to the safety of trial participants and/or data reliability. Whenever local regulations/guidelines allowed remote monitoring was focused on review of critical trial site documentation and source data related to efficacy and safety endpoints.
Parameters with QTLs were established to identify systematic observations that could impact subject safety and/or reliability of trial results. The QTLs were not exceeded in the course of the trial.
The FDA's Assessment:
In general, the data quality of the study appeared acceptable with no errors identified for the major study endpoints.

Efficacy Results – Secondary and other relevant endpoints

Data:
Important secondary efficacy endpoints assessed in the aNHL Expansion Part of the GCT3013-01 trial included CR rate, DOR, DOCR, PFS, and TTR as assessed by IRC using the Lugano criteria (Cheson et al, 2014), as well as MRD negativity, TTNT and OS.
CR Rate:
The CR rate as assessed by IRC was 38.9% (95% CI: 31.2, 46.9) in subjects with LBCL (Table 34).
TTR:
The median TTR was 1.4 months (range: 1.0, 8.4) and median TTCR was 2.7 months (range: 1.2, 11.1) in subjects with LBCL, correlating with the first and second post-baseline scan, respectively. Of the 61 subjects with CR, 36 (59%) had a response that deepened from PR to CR with continued epcoritamab treatment, including 21 (34%) subjects who achieved this deepening of response from PR to CR after 4 months of treatment.
DOR:
After a median follow-up of 10.7 months (range: 0.3, 17.9), the median DOR based on IRC assessment determined by Lugano criteria was 12.0 months (95% CI: 6.6, NR) in all responders with LBCL, with an estimated approximately 60% remaining in response at 6 and 9 months (Figure 12). Furthermore, in LBCL subjects who attained a CR, the median DOR was not reached (95% CI: 12.0, NR), with an estimated approximately 88% remaining in response at 6 and 9 months. DOR based on investigator's assessment was consistent with that based on IRC assessment. Updated DOR data, as of a 30 Jun 2022 data cutoff date, are provided in the Additional Analyses Conducted on the Individual Trials subsection of Section 8.1.2.

Figure 12: Applicant – Kaplan-Meier Plot of Duration of Response Assessed Based on IRC Assessment, Lugano Criteria – GCT3013-01 aNHL Cohort, Expansion Part (Full Analysis Set)



Abbreviations: aNHL = aggressive B-cell non-Hodgkin lymphoma; CI = confidence interval; DLBCL = diffuse large B-cell lymphoma
Data cutoff date: 31 JAN 2022
Source: GCT3013-01-EXP-aNHL CSR Figure 14.2.1.9.1

PFS:

Median PFS (primary definition with PFS censored at the last evaluable tumor assessment on or prior to the date of subsequent anti-lymphoma therapy) was 4.4 months (95% CI: 3.0, 7.9) in subjects with LBCL. Approximately 40% of subjects with LBCL were estimated to remain progression-free at 6 and 9 months.

Non-responders (N=58) progressed early, as evidenced by a median PFS of 1.2 months (95% CI: 1.1, 1.4), whereas for subjects who achieved a PR (N=38), median PFS was 4.0 months (95% CI: 3.0, 4.6). The median PFS in subjects with CR was not reached (95% CI: 14.5 months, NR).

MRD Negativity:

MRD negativity was evaluated as a marker for depth of response. Results from an exploratory analysis of circulating tumor DNA levels in subjects with LBCL showed that 45.8% subjects (95% CI: 36.1, 55.7) achieved MRD-negative status (defined as at least 1 on-treatment MRD-negative sample) in the MRD-evaluable analysis set (N=107). Subjects who achieved MRD-negative status had substantially improved PFS and OS compared to subjects who were MRD-positive, supporting an association between MRD-negativity and improved long-term efficacy outcomes with epcoritamab monotherapy.

TTNT:

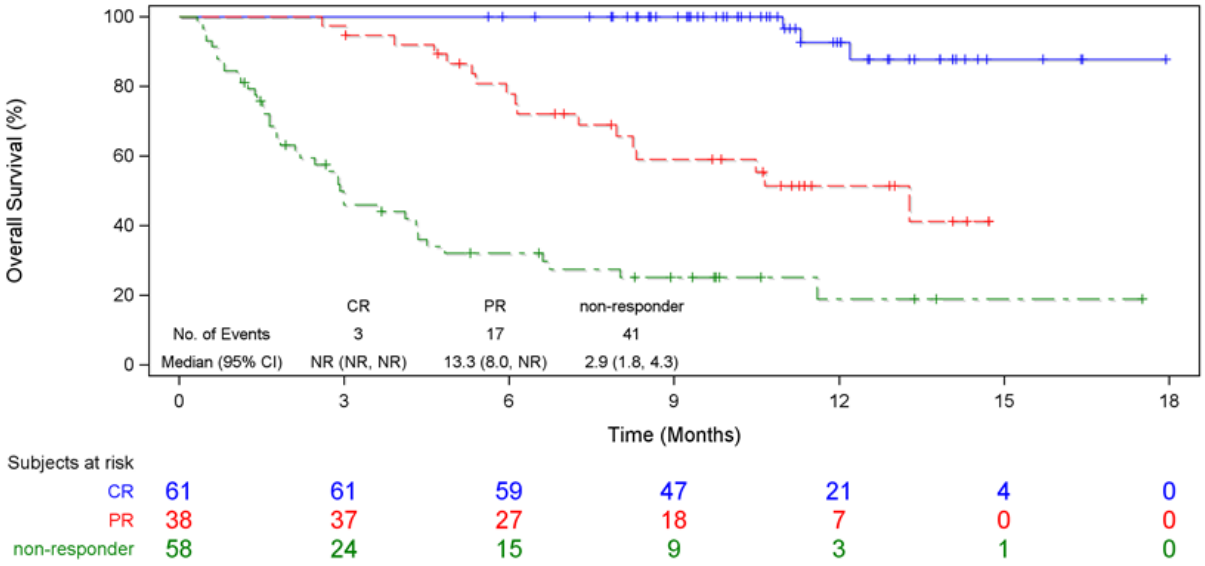
For subjects with LBCL, the median TTNT was 7.4 months (95% CI: 5.9, 10.8) and the estimated percentage of subjects not initiating subsequent therapy at 3, 6, and 9 months was 73.5%, 58.0%, and 48.1%, respectively. TTNT has utility as a surrogate marker for duration of clinical benefit.

OS:

After a median follow-up of 10.7 months (range: 0.3, 17.9), the median OS was not reached (95% CI: 11.3, NR) for subjects with LBCL. The estimated percentage of subjects with LBCL who remained alive at 6 and 12 months was approximately 70% and 56%, respectively.

Notably, among the 61 subjects assessed as complete responders by IRC in GCT3013-01 LBCL, a total of 3 subjects died by the data cutoff date of 31 Jan 2022. In an exploratory, post-hoc Kaplan-Meier analysis, the median OS for subjects who achieved CR was not reached and the estimated 9-month and 12-month OS rates were 96.6% and 92.7%, respectively (Figure 13). The median OS was 13.3 months (95% CI: 8.0, NR) for subjects who achieved PR and 2.9 months (95% CI: 1.8, 4.3) in non-responders.

Figure 13: Applicant – Kaplan-Meier Plot of Overall Survival by Best Overall Response based on IRC Assessment, Lugano Criteria – GCT3013-01 Expansion Part - Subjects in aNHL Cohort (Full Analysis Set)



Abbreviations: aNHL = aggressive B-cell non-Hodgkin lymphoma; CI = confidence interval; CR = complete response; PR = partial response; NR = not reached.
Data cutoff date: 31 Jan 2022
Source: GCT3013-01-EXP-aNHL CSR Figure 14.2.1.13.5

Efficacy Evaluation in Subjects with Other aNHL Subtypes:

The summary tables for efficacy evaluations combine the 18 subjects who had LBCL subtypes

other than DLBCL at trial entry into 1 group, designated “other subtypes”. Responses achieved by other histological subtype of LBCL are as follows:

- Among the 5 subjects with FL grade 3B, 3 had a CR and 2 had a PR.
- Among the 9 subjects with HGBCL NOS, 4 had a PR, 1 had SD, and 4 had PD.
- Among the 4 subjects with PMBCL, 2 had a CR and 2 had a PR.

As presented above, efficacy results for subjects with DLBCL (N=139) were comparable to those for subjects with LBCL overall (N=157).

Efficacy Evaluation in Subjects with HGBCL with MYC and BCL2 and/or BCL6 Rearrangements in the Pivotal GCT3013-01 aNHL Expansion Cohort:

A retrospective, central laboratory FISH analysis was performed on available diagnostic baseline tumor tissue sections from subjects in the aNHL expansion cohort to identify subjects with DH/TH lymphoma.

Based on central laboratory FISH analysis of screening tumor tissue available from 88 subjects enrolled as having DLBCL, 12 (13.6%) subjects had tumors with MYC and BCL2 and/or BCL6 rearrangements (ie, DH or TH lymphoma). These 12 subjects are classified as having HGBCL with MYC and BCL2 and/or BCL6 rearrangements according to the WHO 2016 criteria (Swerdlow et al., 2016); hereafter, this subgroup is referred to as “HGBCL by FISH”. Efficacy analyses were performed on the subjects with HGBCL by FISH (N=12) alone and in combination with the 18 subjects who were enrolled as having “other LBCL subtypes” based on histology at trial entry. These 30 subjects (referred to as “HGBCL by FISH + other LBCL subtypes”) represent a broader subgroup of subjects who have LBCL subtypes, including HGBCL NOS, HGBCL with MYC and BCL2 and/or BCL6 rearrangements, PMBCL, or FL3B.

The ORR based on IRC assessment in subjects with HGBCL by FISH (n=12) was 50.0% (95% CI: 21.1, 78.9), with a CR rate of 33.3% (95% CI: 9.9, 65.1). Among this subgroup (n=12), the median DOR among all responders was 12.0 months (95% CI: 1.1, NR), with 83.3% of subjects remaining in response at 6 and 9 months. The median DOR among complete responders was 12.0 months (95% CI: NR, NR), with 100.0% of subjects remaining in response at 6 and 9 months.

The ORR in the broader subgroup of subjects with HGBCL by FISH + other LBCL subtypes (N=30) was 63.3% (95% CI: 43.9, 80.1), with a CR rate of 36.7% (95% CI: 19.9, 56.1). Among this subgroup (n=30), the median DOR among all responders was 12.0 months (95% CI: 1.9, NR) with 65.7% of subjects remaining in response at 6 and 9 months. The median DOR among complete responders was 12.0 months (95% CI: NR, NR) with 100.0% of subjects remaining in response at 6 and 9 months.

These results were comparable to results in subjects with LBCL (N=157), who had an ORR of 63.1% (95%: 55.0, 70.6) with a CR rate of 38.9% (95% CI: 31.2, 46.9). DOR values were also comparable to the results in subjects with LBCL (N=157), with a median DOR among all responders of 12.0 months (95% CI: 6.6, NR) and a median DOR among complete responders not reached (95%: 12.0, NR).

The Applicant's Position:
Overall, epcoritamab induced deep and durable responses in subjects with R/R LBCL, including other LBCL subtypes, and demonstrated clinically meaningful activity in subjects with PMBCL, FL 3B, and HGBL including DH/TH lymphoma.

The FDA's Assessment:
The FDA agrees with the Applicant's position and has provided the following additional information.

Durability of Response:
With a median follow-up for DOR of 10.7 months, the estimated median DOR was 12.0 months (95% CI: 6.6, not reached). In all responders with LBCL, approximately 60% remained in response at 6 and 9 months. These findings suggest that response following epcoritamab is durable. However, this DOR data is limited in regard to response follow-up. While the median follow-up of all patients was 10.5 months, based on the ADEFFTTE dataset supplied by the Applicant, the FDA calculated the median DOR follow-up in the 99 responders as 7.2 months (range: 0.03 to 15.5), resulting in 67% of patients with a response followed for at least 6 months. For the DOR data to be considered informative in patients with aggressive lymphoma, the FDA recommends that all responders are followed for a minimum of 6 months following the achievement of an objective response. Because of this limitation, the Applicant provided updated DOR data with a data cutoff of 30 June 2022. See the Additional Analyses Conducted on the Individual Trials subsection of Section 8.1.2.

Time to event endpoints: PFS, OS
FDA considers the time to event endpoints, including progression-free survival and overall survival, as not interpretable in single-arm trials. This is due in part to the lack of a natural benchmark for such endpoints.

Response According to Subtype of LBCL
The FDA analysis also examined the responses based on LBCL subtype following the reclassification using central laboratory FISH analysis. This analysis is shown in the table below. As stated previously, interpretation of epcoritamab response is limited in subtypes of LBCL other than DLBCL due to enrollment of few patients with each diagnosis. Re-classification by FISH increased HGBCL patient numbers from 9 to 21. Based on the revised incidence of 21 patients, the data are adequate to inform efficacy in patients with HGBCL in the context of the totality of data. Factoring in the limitations that the response analysis of this reclassified HGBCL subtype was not prespecified and still contains an overall small sample size, the response findings observed suggest a favorable activity of epcoritamab in this difficult to treat subtype and support inclusion of HGBCL along with DLBCL in the final indicated patient population.

Table 36: FDA Summary of Response According to Subtype of LBCL

Diagnosis	Primary Safety Population n, (%) [95% CI]	
	ORR	CR
Diagnosis prior to FISH analysis		
LBCL n=157	99 (63) [55.0, 70.6]	61 (39) [31.2, 46.9]
DLBCL n=139	86 (62) [53.3, 70.0]	54 (39) [30.7, 47.5]
HGBCL n=9	4 (44%) [13.7, 78.8]	2 (22%) [2.8, 60.0]
FL Grade 3B n=5	5 (100) [47.8, 100]	3 (60) [14.7, 94.7]
PMBCL n=4	4 (100) [39.8, 100]	2 (50) [6.8, 93.2]
Diagnosis after FISH analysis		
DLBCL n=127	80 (63) [54.0, 71.4]	50 (39) [30.8, 48.4]
HGBCL n=21	10 (48) [25.7, 70.2]	6 (29) [11.3, 52.1]
Source: FDA Analysis		

Dose/Dose Response

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Data:
N/A

The Applicant's Position:
N/A

The FDA's Assessment:
Not applicable

Durability of Response

Data:
DOR, PFS, OS, and TTNT are presented as secondary endpoints. See Section 8.1.2 for the

secondary endpoints.

The Applicant's Position:
N/A

The FDA's Assessment:
The FDA confirms that DOR, PFS, OS, and TTNT are presented as secondary endpoints.

Persistence of Effect

Data:
Of the 61 subjects in the aNHL Expansion Part of the GCT3013-01 trial who had a CR, 8 subsequently died or had PD as of the 31 Jan 2022 data cutoff date. Among these 61 subjects, the 6 and 9 month DOR rate was 88%.

The Applicant's Position:
The CR rate and DOR in subjects with a CR provide supportive evidence of epcoritamab persistence of effect.

The FDA's Assessment:
The FDA agrees with the Applicant's position that the DOR in patients with a CR provide supportive evidence of epcoritamab persistence of effect.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

Data:
Six questions from the FACT Lym questionnaire (P2 [body pain], BRM3 [fever], ES3 [night sweats], GP1 [lack of energy], BMT6 [tires easily], and C2 [weight loss]) were considered related to key symptoms of lymphoma and changes in those symptoms from baseline were secondary endpoints for the pivotal aNHL Expansion Part of the GCT3013-01 trial. While on treatment, marked improvements (reflected in improvements in the means of the individual item scores) were observed in all 6 PROs (body pain, fever, night sweats, lack of energy, tires easily, and weight loss) from C2D1 to C13D1 (the latest time point that included ≥20 subjects with LBCL). Additional PROs were explored using the subscales of the FACT-Lym questionnaire (ie, the lymphoma subscale [FACT-LymS], trial outcome index (TOI), the FACT-G, and FACT-Lym Total Score) and the Euroqol quality of life questionnaire (EQ 5D 3L) with the related VAS. These analyses were exploratory endpoints in the aNHL Expansion Part of the GCT3013-01 trial. Across all these PRO measures, consistent patterns of improvement were observed, with improvements that exceeded the minimally important differences in the FACT-LymS and the VAS. The quantitative improvements in patient reported outcomes while on treatment were supported by findings from qualitative exit interviews with patients (n=20) reporting

improvements in symptoms, satisfaction with epcoritamab treatment, and that they found the treatment tolerable and convenient.

The Applicant's Position:
Consistent patterns of improvements in PROs were observed in the FACT-Lym questionnaire subscales and the EQ-5D-3L, with improvements that exceeded the minimally important differences in the FACT-LymS and the VAS.

The FDA's Assessment:
The FDA acknowledges the descriptive improvements in patient-reported outcomes. However, the single-arm, open-label trial design limits the PRO data interpretation since a patient's knowledge of treatment regimen may lead to systematic overestimation or underestimation of the treatment effect. The PRO data were considered as supportive data for this application.

Additional Analyses Conducted on the Individual Trial

Data:
As of the 30 Jun 2022 data cutoff date, the updated median DOR (as assessed by IRC using Lugano criteria) was 15.5 months (95% CI: 9.7, NR) in all responders with LBCL (with a median DOR follow-up time of 9.8 months). The estimated percentage of responders remaining in response at 6, 9, and 12 months was 65.3%, 61.2%, and 55.1%, respectively. In those subjects with LBCL who attained a CR, the median DOR was 17.3 months (95% CI: 15.6, NR). The estimated percentage of complete responders with LBCL remaining in response at 6, 9, and 12 months was 92.9%, 88.7%, and 79.1%, respectively.
The Applicant's Position:
Updated IRC-assessed efficacy data from the pivotal aNHL expansion cohort of Study GCT3013-01, as of a 30 Jun 2022 data cutoff date, are provided with the submission to provide longer follow-up of DOR for all responders, in particular for subjects achieving CR.

The FDA's Assessment:
The FDA agrees with the Applicant's analysis results based on 30 June 2022 cutoff data for DOR. These results provide an additional 5 months of follow-up over the cutoff for the primary analysis (31 Jan 2022). The updated data provide longer follow-up of DOR for all responders including patients achieving CR.

In patients with LBCL, a median follow-up for response of at least 6 months for all responders is recommended to ensure the DOR data is mature and adequate to inform the assessment of the durability of a therapy. The additional 5-month follow-up data resulted in an updated median follow-up of DOR in the 99 responders of 9.8 months with approximately 81% of patients with response followed for at least 6 months. Thus, the increase in the median DOR from an initial 12 months to 15.5 months in the context of a more mature DOR data supports the durability of

responses obtained following epcoritamab therapy in the indicated population.

8.1.3. DLBCL Expansion Cohort of Supportive Trial GCT3013-04

Design

The Applicant's Description:
Study Design
This is an open-label, single-country, interventional, multicohort, phase 1/2 trial in Japanese subjects with R/R B-NHL. The trial consists of 2 parts: a Dose Escalation Part (enrolling up to 18 evaluable subjects), and an Expansion Part comprised of a Monotherapy Part (including a DLBCL cohort that enrolled 36 subjects) and a Combination Therapy Part. Efficacy analyses to support this submission include subjects from the DLBCL cohort of the Monotherapy Expansion Part (hereafter referred to as the DLBCL expansion cohort) of the trial only (enrollment complete and ≥6 months follow up from the last subject's first dose).
The Dose Escalation Part of the trial was performed using a modified 3+3 design to determine the epcoritamab RP2D in Japanese subjects. Full doses of 24 mg and 48 mg epcoritamab were evaluated. Selection of 48 mg as the full dose level of epcoritamab for the RP2D regimen was based on PK/pharmacodynamic modeling and supported by all available data (PK, pharmacodynamics, safety, and efficacy) from the Dose Escalation Part of GCT3013-04 and from GCT3013-01.

Trial Location
The dose escalation part was conducted across 6 sites in Japan. The DLBCL expansion cohort was conducted across 15 sites in Japan.

The FDA's Assessment:
The FDA agrees with the Applicant's description of the study design. The primary efficacy analysis conducted by the FDA focused on the 157 patients with R/R LBCL in the expansion part of the pivotal trial GCT3013-01. Study GCT3013-04 is a single-country, open-label, multicohort trial, conducted only in Japanese patients with R/R B-NHL. The FDA considers the results of this trial as supportive given the single country nature of the trial and potential limited applicability to a U.S. patient population.

Eligibility Criteria

The Applicant's Description:
The DLBCL expansion cohort of the GCT3013-04 trial enrolled Japanese subjects with R/R DLBCL similar to those enrolled in the aNHL expansion cohort of the GCT3013-01 trial.

The FDA's Assessment:
The FDA agrees with the Applicant's description of the eligibility criteria.

Study Endpoints

The Applicant's Description:
Primary Endpoints

- ORR as determined by Lugano criteria as assessed by Independent Response Committee (IRC)

Secondary Endpoints

- CR rate, DOR, PFS, DOCR, TTCR, and TTR as determined by Lugano criteria as assessed by IRC
- TTNT
- OS
- Safety (ie, AEs, laboratory parameters, and cytokine measures)
- PK parameters (clearance, volume of distribution, $AUC_{0\text{-last}}$ and $AUC_{0\text{-}\infty}$, C_{max}, t_{max}, predose concentrations, and $t_{½}$), and incidence of ADAs to epcoritamab
- Rate and duration of minimal residual disease (MRD) negativity

The FDA's Assessment:
The FDA agrees with the Applicant's description of the primary endpoint and secondary endpoints. Data provided by the applicant regarding the primary and secondary endpoints from patients in Study GCT3013-04 is considered supportive.

Statistical Analysis Plan and Amendments

The Applicant's Description:
No formal hypothesis testing was performed. Analyses of trial participants and efficacy were performed using the Full Analysis Set (FAS), defined as all subjects who had been exposed to epcoritamab. Analysis of safety was performed using the Safety Analysis Set, which was identical to the FAS.

Sample Size
A response rate greater than 35% for Japanese subjects with DLBCL was considered indicative of both clinical relevance and consistency with earlier results. A sample size of 35 subjects was selected for the DLBCL expansion cohort. Therefore, at least 13/35 (37%) subjects would need to respond to treatment, to have the desired ORR of greater than 35%. The probability of observing at least 13 responders, under the assumption that the true ORR is 45%, is 87%.

Efficacy and Safety
In the Monotherapy Expansion Part, response to study treatment and disease progression was centrally reviewed by an IRC, in addition to investigator evaluation, based on Lugano criteria. Date of PD was defined as the earliest date of documented progression after which there was

no more PR or CR assessment.
Continuous data were summarized using descriptive statistics such as mean, standard deviation, median, and range. Categorical data were summarized using frequency count as well as 95% exact confidence interval (CI), if applicable. For time to event data, the Kaplan-Meier method was used for descriptive summaries. Sensitivity analyses were performed for the DLBCL expansion cohort using additional predefined analysis populations.
Changes from Originally Planned Analysis
Due to missing baseline tumor biopsies, subject consent preference, and/or unevaluable assay results, all exploratory MRD analyses were performed using the MRD-evaluable subset, including subjects who had at least one on treatment MRD sample. In addition, exploratory MRD analysis was performed using ctDNA instead of peripheral blood mononuclear cell (PBMC) results due to inadequate sensitivity of the PBMC assay.
Neutralizing antibodies against epcoritamab were not evaluated at this time due to the low incidence of samples positive for antibodies to epcoritamab. Flow cytometry assays were not performed due to logistical challenges.

The FDA's Assessment:
The FDA agrees with the Applicant's statistical analysis plan and sample size calculation. The 35% ORR rate was considered as a benchmark based on therapies with regular approval or standard of care regimens to inform the proposed sample size. The FDA notes that the study was powered to ensure that the point estimate of ORR exceeded 35% rather than the lower bound of the associated confidence interval.

Protocol Amendments

The Applicant's Description:
A total of 3 protocol amendments were made to the original protocol (dated 20 May 2020, protocol version 1.0). No subjects were enrolled under the original protocol. A summary of key changes with each amendment is provided in Table 37.

Table 37: Applicant – Protocol Amendments for GCT3013-04

Amendment Number	Issue Date	Key Changes
Amendment 1, version 2.0	01 Jul 2020	Based on regulatory authority feedback, the protocol was amended to clarify details around hepatitis testing, DLT criteria, the requirement for pharmacogenomic sample collection, and safety reporting. In addition, a correction to the contraception table was made. • Added a new DLT criterion: any AE considered related to epcoritamab treatment that causes a delay in dosing of >7 days. • Clarified that all subjects must consent to the collection and use of MRD samples to participate in this trial. • Clarified that there is no interaction between epcoritamab and hormonal contraception. • Allowed a window of time for collection of PK samples collected after the 24-hour time point. • To improve clarity, additional details regarding evaluation of events occurring during the DLT evaluation period were added. • Clarified that for subjects with chronic infection, testing for hepatitis B must be negative prior to treatment with epcoritamab, and would be monitored monthly throughout the trial.
Amendment 2, version 3.0	11 Mar 2021	Updates to the protocol were made to change to a commercially available saline solution as diluent, make corrections and clarifications, to allow a 6-week interruption in epcoritamab treatment, to provide details of requirements for pre-medication and CRS prophylaxis, and to align with program protocols. • Implemented mandatory bone marrow biopsy requirement for all subjects at screening. • Deleted HIV from visit assessment schedules; modified HIV exclusion criterion. • Added ECOG performance status score ≤2 to the inclusion criteria. • Added information on management for chronic infection with hepatitis B.

Amendment Number	Issue Date	Key Changes
Amendment 3, version 4.0	02 Dec 2021	The overall rationale of this amendment was applicable to the Combination Therapy Expansion Part. The changes applicable to the Dose Escalation and Monotherapy Expansion Part included: • For the Dose Escalation Part, clarified that ORR, CR rate, DOR, and PFS determined by Lugano criteria would be assessed by the investigator rather than the IRC. • For the Monotherapy Expansion Part, added DOCR, TTCR, and TTR assessed by the IRC to the secondary endpoints for anti-lymphoma efficacy determined by Lugano. • For the Monotherapy Expansion Part, the following process was removed: expedited IRC review and confirmation of investigator-assessed PD according to Lugano. This was originally implemented to avoid premature discontinuation in case of pseudoprogression. • Removed "hospitalizations" as a secondary safety endpoint. • Added an exclusion criterion that SARS-CoV-2 vaccine should not be administered during the 28-day period prior to initiation of epcoritamab or during Treatment Cycle 1. • Added that biomarker assessments would also be performed to explore the relationship to efficacy or mechanism of action of epcoritamab.

Abbreviations: AE = adverse event; CR = complete response; CRS = cytokine release syndrome; DLBCL = diffuse large B-cell lymphoma; DLT = dose-limiting toxicity; DOCR = duration of complete response; DOR = duration of response; ECOG = Eastern Cooperative Oncology Group; FL = follicular lymphoma; HIV = human immunodeficiency virus; IRC = Independent Review Committee; MRD = minimal residual disease; ORR = overall response rate; PD = progressive disease; PFS = progression-free survival; PK = pharmacokinetic(s); TTCR = time to complete response; TTR = time to response.

The FDA's Assessment:

The FDA agrees with the summary of Protocol Amendments for GCT3013-04. Data supplied by the Applicant pertaining to this study is considered supportive.

8.1.4. Study Results: DLBCL Expansion Cohort in Supportive Trial GCT3013-04

Compliance with Good Clinical Practices

Data:

Investigator sites and service provider audits were conducted to assess compliance with GCP. Site audits were conducted undertaking a risk-based approach. Two sites (JP003 and JP010) have been audited at the time of the database lock. In addition, selected vendors have been audited. A consolidated audit certificate is included in Appendix 16.1.8 of the protocol.

The Applicant's Position:
This trial was conducted in compliance with the International Council for Harmonisation Good Clinical Practice, ICH GCP E6(R2), standards stipulated in Article 14, Paragraph 3, and Article 80-2 of the "Law on Securing Quality, Efficacy and Safety of Products including Pharmaceuticals and Medical Devices," Ministerial Ordinance on Good Clinical Practice for Drugs – Ordinance of the Ministry of Health and Welfare (J-GCP), Principles of the Declaration of Helsinki, and applicable regulatory requirements. Generally, the priority was given to J-GCP for definitions of terminology and other minor differences between J-GCP and ICH GCP.

The FDA's Assessment:
The FDA agrees with the Applicant's summary of compliance with good clinical practice.

Financial Disclosure

The Applicant's Position:
As accepted at the Type C meeting on 08 Dec 2021, the Sponsor is providing Bioresearch Monitoring (BIMO) datasets only for the pivotal trial GCT3013-01 R/R aNHL cohort, which provides the primary efficacy and safety data for the Agency to evaluate epcoritamab's benefit-risk profile.

The FDA's Assessment:
As data from GCT3013-04 is supportive, the FDA agrees with the Applicant's position.

Patient Disposition

Data:
In the DLBCL expansion cohort, a total of 36 subjects received at least one dose of epcoritamab. As of the data cutoff date of 31 Jan 2022, 22 (61.1%) subjects discontinued epcoritamab treatment and 14 (38.9%) were continuing on epcoritamab treatment.
The most frequent reason for treatment discontinuation was progressive disease in 20 (55.6%) subjects (6 subjects with clinical progression, which was confirmed by imaging, and 14 subjects with disease progression according to response criteria), and 2 (5.6%) subjects discontinued treatment due to AE (both due to second primary malignancies not considered related to epcoritamab by the investigator).
A total of 13 (36.1%) subjects permanently discontinued the trial, all due to death.

The Applicant's Position:
The majority of patients discontinued treatment due to progressive disease (55.6%).

The FDA's Assessment:
The FDA acknowledges the data supplied by the Applicant and notes that this information is supportive.

Protocol Violations/Deviations

Data:
Two (5.6%) subjects in the DLBCL expansion cohort had an important protocol deviation noted: 1 subject with an eligibility and entry criteria deviation (C1D1 neutrophil count did not meet eligibility criteria), and 1 subject with a trial procedure deviation (CRS prophylactic corticosteroid not administered prior to C1D24 dose).

The Applicant's Position:
The deviations that occurred in the DLBCL expansion cohort of the GCT3013-04 trial were assessed to have negligible impact on the overall interpretation of the trial results.

The FDA's Assessment:
The FDA agrees with the Applicant's position.

Table of Demographic Characteristics

Data:
Demographic characteristics are provided in Table 38 for the DLBCL expansion cohort.

Table 38: Applicant – Demographic Characteristics – GCT3013-04 DLBCL Cohort, Monotherapy Expansion Part (Full Analysis Set)

Demographic Parameters	DLBCL Cohort (N=36)
Sex	
Male	17 (47.2%)
Female	19 (52.8%)
Age	
Mean years (SD)	68.5 (8.22)
Median (years)	68.5
Min, max (years)	44, 89
Age Group	
<65 years	10 (27.8%)
65 to <75 years	18 (50.0%)
≥75 years	8 (22.2%)

Race	
Asian	36 (100.0)
Ethnicity	
Not Hispanic or Latino	36 (100.0)

Abbreviations: max = maximum, min = minimum, SD = standard deviation.
Note: All subjects were of Asian race and Japanese ethnicity.
Source: GCT3013-04 Primary CSR Table 14.1.1.2.b.

The Applicant's Position:
All subjects were of Asian race and Japanese ethnicity as required per protocol.

The FDA's Assessment:
The FDA acknowledges the data supplied by the Applicant and notes that this information as it pertains to Study GCT3013-04 is considered supportive.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Data:
Baseline disease characteristics are summarized in Table 39 for the DLBCL expansion cohort. Prior anti-lymphoma therapies are summarized in Table 40.

Table 39: Applicant – Baseline Disease Characteristics – GCT3013-04 DLBCL Cohort, Monotherapy Expansion Part (Full Analysis Set)

	DLBCL Cohort (N=36)
Disease type at trial entry	
DLBCL	36 (100.0%)
De novo	30 (83.3%)
Transformed	6 (16.7%)
Disease type at initial diagnosis: FL	6 (16.7%)
DLBCL cell-of-origin classification	
Germinal center B-cell (GCB)	8
Non-germinal center B-cell (non-GCB)	16
Unknown	4
Not done	1
Median time (min, max) from initial diagnosis to 1st dose[a], years	2.177 (0.33, 16.12)
Subjects with chromosomal alteration per local laboratory	
Number evaluable	7
Double-hit lymphoma	1
Triple-hit lymphoma	0
Ann Arbor stage at screening	
Stage I	2 (5.6%)

	DLBCL Cohort (N=36)
Stage II	6 (16.7%)
Stage III	9 (25.0%)
Stage IIIE	1 (2.8%)
Stage IV	18 (50.0%)
IPI (at trial entry)	
0-2	13 (36.1%)
≥3	23 (63.9%)
Presence of any constitutional symptoms	2 (5.6%)
Night sweats	1 (2.8%)
Weight loss (>10% over last 6 months)	1 (2.8%)
Fever	0
Extreme fatigue	0

Abbreviations: DLBCL = diffuse large B-cell lymphoma; FL = follicular lymphoma; IPI = International Prognostic Index; max = maximum; min = minimum.

Note: DLBCL cell of origin classification for 7 subjects was missing.

[a.] Time from diagnosis of disease recorded at time of trial entry.

Data cutoff date: 31 Jan 2022

Source: GCT3013-04 Primary CSR Table 14.1.1.3.b

Table 40: Applicant – Prior Anti-lymphoma Therapies – GCT3013-04 DLBCL Cohort, Monotherapy Expansion Part (Full Analysis Set)

Number of Subjects, n (%)	DLBCL Cohort (N=36)
Prior radiotherapy	14 (38.9%)
Prior stem cell transplant	7 (19.4%)
ASCT	7 (19.4%)
Subject relapsed ≤12 months after ASCT	3 (8.3%)
Prior systemic therapy received	
Anti-CD20	36 (100.0%)
Anti-CD19	0
Alkylating agents	36 (100.0%)
Anthracyclines	35 (97.2%)
Nucleotide	26 (72.2%)
Topoisomerase inhibitor	27 (75.0%)
PI3K inhibitor	0
BCL2 inhibitor	0
Polivy	1 (2.8%)
CAR T-cell therapy	0
Median number (min, max) of prior lines of anti-lymphoma therapy	3.0 (2, 8)
Number of prior lines of anti-lymphoma therapy, n (%)	
2	16 (44.4%)
3	9 (25.0%)
≥4	11 (30.6%)
Median time (min, max) from end of last-line anti-lymphoma therapy to 1st dose, months	2.81 (0.1, 39.3)
Subjects with primary refractory disease[a]	20 (55.6%)
Subjects refractory to ≥2 consecutive lines of prior anti-lymphoma therapy[b]	21 (58.3%)
Last-line systemic antineoplastic therapy response status	
Refractory[b]	29 (80.6%)
No response	21 (58.3%)
Relapsed within 6 months after therapy completion	8 (22.2%)
Relapsed[c]	7 (19.4%)

Abbreviations: ASCT = autologous stem cell transplant; CAR = chimeric antigen receptor; DLBCL = diffuse large B-cell lymphoma; max = maximum; min = minimum.

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

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

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

Data cutoff date: 31 Jan 2022

Source: GCT3013-04 Primary CSR Table 14.1.1.6.1.b.

The Applicant's Position:
The baseline characteristics of subjects in the DLBCL expansion cohort were consistent with a heavily pre-treated and highly refractory population.

The FDA's Assessment:
The FDA acknowledges the data supplied by the Applicant and notes that this information as it pertains to Study GCT3013-04 is considered supportive.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Data:
Treatment Compliance:
The median relative dose intensity for subjects in the DLBCL expansion cohort was 100% (range: 65, 104) in Cycles 1 to 3 (QW dosing), 100% (range: 86, 101) in Cycles 4 to 9 (Q2W dosing), and 98.7% (range: 93, 100) in Cycle 10+ (Q4W dosing)
Overall, 15 (41.7%) subjects experienced a dose delay during the trial, 14 of these due to TEAEs. One subject required epcoritamab re-priming due to dose delay of approximately 4 weeks. Dose reductions were not allowed in this trial.
Concomitant Medications:
The categories of most commonly used (by ≥50% of subjects) concomitant medications in the DLBCL expansion cohort were antibacterials (100%), analgesics and drugs for acid-related disorders (88.9% each), blood substitutes and perfusion solutions (75.0%), systemic antivirals (72.2%), drugs for constipation (69.4%), and systemic corticosteroids (50.0%).
Per protocol, premedication with a corticosteroid, antihistamine, and antipyretic and posttreatment CRS prophylaxis with a corticosteroid were mandatory during Cycle 1 of treatment. The use of corticosteroids, anti-cytokine therapy, or other supportive therapies for the treatment of CRS or ICANS is summarized in Section 8.2.5.
Rescue Medication Use:
There are no reversal agents for epcoritamab.

The Applicant's Position:
Subjects' compliance to study drug allowed adequate assessment of safety and efficacy of subjects in this trial population.

The FDA's Assessment:
The FDA acknowledges the data supplied by the Applicant and notes that this information as it pertains to Study GCT3013-04 is considered supportive.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

Data:

The primary efficacy endpoint in the DLBCL expansion cohort (N=36), ORR by IRC assessment using Lugano criteria, was 55.6% (95% CI: 38.1, 72.1) with 44.4% (N=16) and 11.1% (N=4) in subjects achieving best response of CR and PR, respectively.

The Applicant's Position:
Treatment with epcoritamab induced deep responses in adult Japanese patients with R/R DLBCL, confirming the efficacy of epcoritamab in an independent trial.

The FDA's Assessment:

Among the 36 Japanese patients, the ORR per IRC was 56% (95% CI: 38, 72), with 44% achieving best response of CR. The efficacy data observed in the GCT3013-04 study was consistent with that of pivotal GCT3013-01 study and can be considered supportive of epcoritamab activity in the indicated population.

One limitation of this study is the use of the single-arm trial design. In single-arm trials, the efficacy assessment will be based on the lower limit of a 95% confidence interval to exceed a clinically relevant response rate. While this study was not powered for this aim, the FDA notes that the lower limit of 95% CI of ORR was 38%, which is higher than 35% ORR rate in the null hypothesis. The null hypothesis was only used to inform the sample size.

The FDA notes that patients with subtypes of LBCL other than DLBCL were not enrolled in the GCT3013-04 study. Therefore, the evidence of efficacy for such patients is limited to trial GCT3013-01.

As noted above, there is no formal scientific definition of "deep responses" and would consider such language to be misleading.

Data Quality and Integrity

Data:
N/A

The Applicant's Position:
This trial was conducted in compliance with ICH GCP E6(R2) and applicable regulatory requirements. Steps were taken to ensure the accuracy and reliability of data included the selection of qualified investigators and appropriate trial sites, review of protocol procedures with the investigator and trial site personnel before the trial, periodic monitoring visits by the sponsor, and direct transmission of data from vendors into the sponsor's data base. Written instructions were provided for collection, handling, storage, and shipment of samples.

Clinical research associates conducted site visits to the investigational facilities for the purpose of monitoring various aspects of the trial. Instructions for data entry and completion were provided in the eCRF completion guidelines.
During the trial, the COVID-19 pandemic significantly impacted the possibility of on-site monitoring. A risk-based approach was implemented and on-site monitoring and central monitoring focused on critical data /processes essential to the safety of trial participants and/or data reliability. Whenever local regulations/guidelines allowed remote monitoring was focused on review of critical trial site documentation and source data related to efficacy and safety endpoints.
Parameters with QTLs were established to identify systematic observations that could impact subject safety and/or reliability of trial results. The QTLs were not exceeded in the course of the trial.

The FDA's Assessment:
The FDA agrees with the Applicant's position. In general, the data quality of the study appeared acceptable with no errors identified for the major study endpoints.

Efficacy Results – Secondary and other relevant endpoints

Data:
After a median follow-up of 8.4 months (range: 1.5, 12.0), the median DOR was not reached. A total of 6 (30.0%) subjects had an event and 14 (70.0%) subjects were censored. The estimated percentage of subjects remaining in response at 6 and 9 months was 69.3% and 59.4%, respectively. In those subjects who attained a CR, the median DOR was not reached. The estimated percentage of subjects remaining in response at 6 and 9 months was 61.9%. Updated DOR data, as of a 30 Jun 2022 data cutoff date, are provided in the Additional Analyses Conducted on the Individual Trials subsection of Section 8.1.4.
A total of 61.1% subjects experienced a PFS event (disease progression or death). The median PFS was 4.1 months (95% CI: 1.2, NR) months. The estimated percentage of subjects remaining progression free at 6 and 9 months was 40.6% and 33.8%, respectively.
Median OS was not reached. The estimated percentage of subjects remaining alive at 6 and 9 months was 70.7% and 59.8%, respectively.
Median TTNT was 5.8 (95% CI: 3.0, NR) months.

The Applicant's Position:
Treatment with epcoritamab induced deep and durable responses in adult Japanese patients with R/R DLBCL.

The FDA's Assessment:

The FDA agrees with the Applicant's analyses results of secondary endpoints of DOR, PFS OS

and TTNT. The FDA also agrees with the analyses results based on the data of a 30 Jun 2022 data cutoff date.

As noted above, time-to-event endpoints are generally not interpretable in single-arm trials.

Dose/Dose Response

Data:
N/A

The Applicant's Position:
N/A

The FDA's Assessment:
Not applicable.

Durability of Response

Data:
DOR, PFS, OS, and TTNT are presented as secondary endpoints. See Section 8.1.4 for the secondary endpoints.

The Applicant's Position:
N/A

The FDA's Assessment:
Not applicable.

Persistence of Effect

Data:
N/A

The Applicant's Position:
N/A

The FDA's Assessment:
Not applicable.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints
Data:

N/A

The Applicant's Position:
N/A

The FDA's Assessment:
Not applicable.

Additional Analyses Conducted on the Individual Trial

Data:
As of the 30 Jun 2022 data cutoff date, the updated median DOR was 13.4 months (95% CI: 4.2, NR) among responders with DLBCL (with a median DOR follow-up time of 10.0 months). The estimated percentage of responders remaining in response at 6 and 9 months was 68.6% at both time points and was 58.8% at 12 months. In those subjects who attained a CR, the median DOR was not reached (95% CI: 4.2, NR). The estimated percentage of complete responders remaining in response at 6 and 9 months was 68.6% at both time points and 54.9% at 12 months.

The Applicant's Position:
Updated IRC-assessed efficacy data from the DLBCL expansion cohort of Study GCT3013-04, as of a 30 Jun 2022 data cutoff date, are provided with the submission to provide longer follow-up of DOR for all responders, in particular for subjects achieving CR.

The FDA's Assessment:
The FDA agrees with the Applicant's position that the updated analyses results based on the data of a 30 Jun 2022 data cutoff date provided longer follow-up of DOR for all responders including patients achieving CR. As in Study GCT3013-01, these results provided for an additional 5 months of follow-up over the initial data cut.

8.1.5. Integrated Review of Effectiveness

The FDA's Assessment:
An integrated assessment of effectiveness was not conducted. Each trial, study GCT3013-01 and study GCT3013-04, was evaluated separately regarding efficacy.

8.1.6. Assessment of Efficacy Across Trials

The aNHL expansion cohort of the GCT3013-01 trial (N=157 subjects) provides the pivotal data supporting the assessment of the efficacy of epcoritamab in subjects with R/R LBCL. These data

are supported by the results Japanese subjects with R/R DLBCL in the Monotherapy Expansion Part of the GCT3013-04 trial (N=36; referred to as 04-DLBCL).

Primary Endpoints

Data:
The ORR (CR+PR) was clinically meaningful and similar between trials at 63.1% (95% CI: 55.0, 70.6) in 01 LBCL overall and 55.6% (95% CI: 38.1, 72.1) in 04 DLBCL.

The Applicant's Position:
In subjects enrolled in the pivotal aNHL expansion cohort, the ORR (PR + CR) as assessed by IRC was clinically meaningful at 63.1% (95% CI: 55.0, 70.6). Similar consistent efficacy results were observed in 04-DLBCL Japanese subjects. Taken together, these data support the clinically meaningful benefit of epcoritamab treatment in a population of LBCL patients with high unmet medical need.

The FDA's Assessment:
The two trials incorporated into the overall assessment of efficacy of epcoritamab in relapsed or refractory LBCL were the aNHL expansion cohort in GCT3013-01 and the DLBCL expansion cohort in GCT3013-01. The core efficacy analysis conducted by the FDA relied on the pivotal primary efficacy population of 157 patients with relapsed or refractory LBCL present in Study GCT3013-01, while the smaller DLBCL expansion cohort in Study GCT3013-04 was considered supportive only. Both studies administered epcoritamab at the same RP2D and, ultimately, in the intended scheduled regimen.

Besides enrollment location, the eligibility criteria were the same for both studies. Most patients were 65 years or older with the median age in Study GCT3013-01 64 years and 68 years in GCT3013-08. Both populations also consisted of patients with advanced stage and heavily pretreated disease, each with a median of 3 prior lines of therapy. Prior therapy was also similar between the two populations, although exposure to prior CAR-T therapy was represented only in the pivotal efficacy population in GCT3013-01.

The primary endpoint in both studies was ORR (PR+CR) by IRC assessment using Lugano criteria. The FDA analysis in the pivotal aNHL expansion cohort in GCT3013-01 demonstrated an ORR as assessed by IRC as 63% (95% CI: 55, 71). This finding was consistent with that observed in the supportive Study GCT3013-04 where ORR by IRC was 56% (95%CI: 38, 72). At the time of the initial data-cut off, patients in the pivotal efficacy population had a median follow-up of 10.7 months and median DOR of 12 months, while patients in the supportive efficacy cohort in GCT3013-04 had a median follow-up of 8.4 months and the median DOR was not reached.

The FDA analysis of both trials identified limitations. Those issues pertaining to the pivotal trial

GCT3013-01 will be discussed in Section 8.1.7. Regarding the GCT3013-04, the major identified limitation is potential inability to generalize the results to a U.S population. Most general patient demographic elements, such as age, and disease characteristics, such as stage and median lines of prior therapy, were similar. However, all patients in this supportive trial were enrolled from Japan. Given this restricted regional enrollment, 100% of patients were Asian, which may result in potential unknown influence of results from intrinsic and extrinsic factors. Additionally, there were also differences in the prior therapies received. While 39% of patients in Study GCT3013-01 had prior CAR T-cell therapy, no patients in Study GCT3013-04 had this prior therapy. Other regimens, such as those containing polatuzumab vedotin, were also less represented in Study GCT3013-04 when compared to the pivotal trial GCT3013-01.

Secondary and Other Endpoints

Data:

Duration of Response:

After a median duration of follow up of 10.7 months (range: 0.3+, 17.9), the median DOR was 12.0 (95% CI: 6.6, NR) months in 01 LBCL and not reached in 04 DLBCL. In 01 LBCL, the estimated percentage of subjects remaining in response at 6 and 9 months was 62.2% and 60.2%, respectively, and similar to the DLBCL cohort. In 04 DLBCL, after a median duration of follow up of 8.4 months (range: 1.5+, 12.0), the estimated percentage of subjects remaining in response at these times was 69.3% and 59.4%, respectively. Given the number of subjects remaining in response, with extended follow up, the DOR is expected to lengthen.
In subjects in 01 LBCL who attained a CR, the median DOR was not reached. The estimated percentage of subjects remaining in response at 6 and 9 months was 88.7%. Similarly, in subjects in 04 DLBCL who attained a CR, the median DOR was not reached, and the estimated percentage of subjects remaining in response at 6 and 9 months was 61.9%. Updated DOR data, as of a 30 Jun 2022 data cutoff date, are provided in the Additional Analyses Conducted on the Individual Trials subsection of Section 8.1.2 for the GCT3013-01 trial and Section 8.1.4 for the GCT3013-04 trial.

Complete Response Rate:

The CR rate was 38.9% (95% CI: 31.2, 46.9) in 01 LBCL and 44.4% (95% CI: 27.9, 61.9) in 04 DLBCL subjects.

Duration of Complete Response:

Median DOCR was 12.0 (95% CI: 9.7, NR) months in 01 LBCL and not reached in 04 DLBCL. In 01 LBCL, the estimated percentage of subjects remaining in CR at 6 and 9 months was 86.3%, and comparable among the DLBCL subjects. In 04 DLBCL, the estimated percentage of subjects remaining in response at these times was 59.6%.

Progression-Free Survival:

The median PFS was 4.4 months (95% CI: 3.0, 7.9) in 01 LBCL and 4.1 months (95% CI: 1.2, NR) in 04 DLBCL. In 01 LBCL, the estimated percentage of subjects remaining progression free at 6 and 9 months was 43.9% and 39.9%, respectively, and these rates were comparable for 04 DLBCL.

Time to Response:
Responses occurred early in treatment, with a median TTR (CR or PR) based on IRC assessment of 1.4 months in 01 LBCL overall and in 04 DLBCL. This time corresponds approximately to the first assessment time point at 6 weeks. Median time to CR was 2.7 months in 01 LBCL and 2.6 months in 04 DLBCL, approximating the timing of the scheduled second assessment at Week 12.

Overall Survival:
After a median duration of follow up of 10.7 months (range: 0.3+, 17.9), 61 (38.9%) subjects in 01 LBCL died and 96 (61.1%) remained alive. The median OS was not reached, and the estimated percentage of subjects remaining alive at 6 and 12 months was 70.6% and 56.9%, respectively.
In 04 DLBCL, after a median duration of follow up of 8.4 months (range: 1.5+, 12.0), median OS was not reached. The estimated percentage of subjects still living at 6 and 9 months was 70.7% and 59.8%, respectively.

Minimal Residual Disease Status:
For 01 LBCL, MRD status was determined as an exploratory analysis of tumor DNA in plasma samples, and because baseline tumor biopsies, subject consent, and/or assay results were not available for all subjects, analysis of MRD status was performed on the MRD-evaluable set (N=107). The MRD-negativity rate for the MRD-evaluable set (N=107) was 45.8% (95% CI: 36.1, 55.7) in 01 LBCL. Subjects who achieved MRD-negative status had improved PFS and OS compared with subjects who were MRD-positive.
For 04 DLBCL using the ctDNA assay, the overall MRD negativity rate among subjects with DLBCL who were MRD-evaluable (N=29) was 58.6% (95% CI: 38.9, 76.5). The median duration of MRD negativity was not reached, and an estimated 100% of subjects (95% CI: 100, 100) remained MRD negative at 6 months. Among subjects within 04 DLBCL who achieved MRD negativity, PFS was prolonged compared to subjects who were MRD-positive. A similar trend was observed when OS was analyzed by MRD negativity status

Time to Next Anti-Lymphoma Therapy:
For 01 LBCL overall, the median TTNT was 7.4 months (95% CI: 5.9, 10.8) and the estimated percentage of subjects not initiating subsequent therapy at 3, 6, and 9 months was 73.5%, 58.0%, and 48.1%, respectively. In 04 DLBCL subjects, the median TTNT was 5.8 months (95% CI: 3.0, NR), and the estimated percentage of subjects not initiating subsequent therapy at 3, 6,

and 9 months was 66.7%, 49.4%, and 49.4%, respectively.

The Applicant's Position:
The efficacy observed with epcoritamab is clinically meaningful, particularly when considering the high-risk, highly refractory patient population treated in the pivotal aNHL expansion cohort of the GCT3013-01 trial and the DLBCL Expansion Cohort of the GCT3013-04 trial.
ORR is a clinically meaningful endpoint, as it is a direct measure of antitumor activity in a single arm trial and an accepted surrogate of clinical effectiveness in this setting. Furthermore, deep responses, as characterized by CR, are generally associated with longer PFS and survival compared with achievement of PR in the LBCL disease setting. Epcoritamab monotherapy resulted in high~~er~~ ORR and deep responses in a large percentage of subjects with R/R LBCL. These responses occurred early in treatment. Responses to epcoritamab were also durable as characterized by long median DOR and DOCR. For the overall population, PFS was driven by the poor outcomes for non-responders, which may be expected for this aggressive disease (Crump et al, 2017). The observed survival benefit is supportive of the overall efficacy associated with epcoritamab even in the setting of a heavily pre-treated and highly refractory patient population.

The FDA's Assessment:

The FDA agrees with the Applicant's analysis results as describe above. However, the PFS, TTR, TTNT, and OS analyses were deemed not interpretable due to the single-arm nature of the trial. The analysis of MRD was deemed exploratory due to the limited number of patients evaluated and current uncertainties regarding use of ctDNA in the assessment of LBCL residual disease

Subpopulations

Data:
Overall, for most subgroups in 01 LBCL and 04 DLBCL, ORR, CR rate, DOR, PFS, and OS were generally consistent with that of the respective overall populations.

The Applicant's Position:
Efficacy results were generally consistent across subgroups by demographic and baseline characteristics, as well as in subgroups with severe, difficult to treat disease. This demonstrates the meaningful efficacy of epcoritamab in subjects with significant unmet need, including elderly, heavily pre-treated, and subjects who had received CAR T-cell therapy.

The FDA's Assessment:
The FDA agrees with the Applicant's position on the efficacy of subpopulations in terms of the

primary endpoint ORR. As noted above, potential heterogeneity in ORR was noted for a few subgroups (e.g., for the prior anti-lymphoma therapy status in GCT3013-01 trial, the ORR for the primary refractory category was 55% (95%CI: 45-65%) and the ORR for other category was 75% (95% CI: 63-88%). FDA notes that the lower bound of the associated confidence intervals generally exceeded the null rate of 35%, even in subgroups where heterogeneity was noted. These confidence intervals were not adjusted for multiplicity and are considered to be descriptive, providing additional context for the main results.

Additional Efficacy Considerations

The FDA's Assessment:
There were no additional efficacy considerations.

8.1.7. Integrated Assessment of Effectiveness

Data:
The results from the aNHL expansion cohort from the pivotal phase 1/2, global, open-label, first-in-human trial GCT3013-01 provides the primary data to support the assessment of efficacy of epcoritamab in subjects with B-cell lymphoma. Additional supportive data are provided from the DLBCL expansion cohort from the GCT3013-04 trial, a phase 1/2 open-label trial to assess the safety and preliminary efficacy of epcoritamab in Japanese subjects with R/R B-cell NHL. However, because GCT3013-04 included subjects only in Japan, the results of the two studies were not merged into an integrated analysis. Efficacy results from the aNHL expansion cohort of the GCT3013-01 trial are presented in Section 8.1.2 and results from the DLBCL expansion cohort of the GCT3013-04 trial are presented in Section 8.1.4. A brief side-by-side presentation of the primary and secondary efficacy results for the two trials is presented in Section 8.1.5.

The Applicant's Position:
Treatment with epcoritamab using the dosing regimen of 0.16 mg priming, 0.8 mg intermediate, and 48 mg full dose resulted in clinically meaningful, deep, and durable responses in subjects with R/R LBCL in both GCT3013-01 and GCT3013-04. Benefit was consistently observed across subgroups of subjects with high unmet need, including elderly subjects, subjects with primary refractory disease, and subjects who have received prior ASCT or CAR T-cell therapy.

The FDA's Assessment:
The core efficacy assessment of epcoritamab was based on the pivotal Study GCT3013-01, an open-label, multi-cohort, single-arm trial that included an expansion cohort of 157 adult patients with relapsed or refractory large B-cell lymphoma who had received at least two prior lines of systemic therapies, including an anti-CD20 monoclonal antibody. The FDA agrees with

the Applicant in that the findings from the DLBCL expansion cohort in the smaller, similar Study GCT3013-04 were generally consistent with those from the pivotal trial and are considered supportive. However, given that this trial was conducted solely in Japan, the results were not merged into an integrated analysis. Thus, for the integrated assessment of efficacy, the section below refers to FDA analysis of the results from the primary efficacy population in the pivotal Study GCT3013-01.

Study GCT3013-01 required patients to have either failed or be ineligible for autologous hematopoietic stem cell transplantation (HSCT) and excluded patients with active infections, history of autoimmune disease, prior allogeneic transplant, CNS lymphoma, or a seizure disorder requiring therapy.

Patients received epcoritamab subcutaneously in 28-day cycles, at step-up dosing in Cycle 1 (0.16 mg on Day 1, 0.8 mg on Day 8, and 48 mg on Day 15 and Day 22), 48 mg weekly in Cycles 2-4, 48 mg every other week in Cycles 5-9, and 48 mg every four weeks from Cycles 10 onwards. Epcoritamab was administered until progressive disease or unacceptable toxicity.

The prespecified primary endpoint was overall response rate as assessed by Independent Review Committee determined by Lugano criteria (Cheson et al, 2014).

Among the patients with relapsed or refractory LBCL, the median age was 64 years (range: 20 to 83 years), 49% were 65 years of age or older, 60% were male, 61% were White, 19% were Asian, 0.6% were Native Hawaiian or Pacific Islander and none were Black or African American, or Hispanic or Latino. A total of 75% of patients had Stage III-IV disease, and 97% of patients had an ECOG performance status of 0 or 1. The patient population was heavily pretreated with a median number of prior therapies of 3 (range: 2 to 11), with 29% receiving 2 prior therapies, 32% receiving 3 prior therapies, and 39% receiving more than 3 prior therapies.

Sixty-one percent of patients had primary refractory disease with all patients having had anti-CD20 antibody with or without an alkylating agent. Almost all patients (98%) had also had a regimen containing anthracyclines. Consistent with the 3 median lines of therapy, patients had been exposed to several other therapies with 4% of patients having received prior anti-CD19 based therapy, 11% prior polatuzumab vedotin, 39% prior CAR-T therapy, and 20% prior autologous stem cell transplant.

For the expansion cohort of 157 patients with R/R LBCL in Study GCT3013-01, the ORR rate as assessed by the IRC was 63% (95% CI: 55, 71), with 39% achieving a complete response (95% CI: 31, 47). At the time of the initial data cut-off, median DOR per Kaplan-Meier was 12.0 months with a median DOR follow-up of 7.2 months. However, this initial DOR data was considered immature as only 67% of patients with a response had been followed for at least 6 months. An

additional 5 months of follow-up was provided by Applicant at the time of BLA submission based on a data cut-off of 30 June 2022. The updated DOR data was considered mature with approximately 81% of responders followed for at least 6 months with a median DOR follow-up of 9.8 months and an increased median DOR of 15.5 months.

Based on the characteristics of the LBCL patient population enrolled in the expansion cohort of Study GCT3013-01, the data support the determination that epcoritamab has clinically meaningful activity with durable responses in patients with relapsed or refractory LBCL after two or more lines of systemic therapy. To support accelerated approval, the efficacy data are considered in the context of available therapy for patients with relapsed or refractory large B-cell lymphoma in the 3rd line setting and beyond. Available therapy includes chemoimmunotherapy options such as bendamustine plus rituximab (BR), gemcitabine or gemcitabine and oxaliplatin (GemOx) with or without rituximab. Additionally, polatuzumab vedotin plus BR or CAR T-cell therapy are available therapies in this setting. In the 3rd line setting and beyond, the ORRs for the chemoimmunotherapy options range from 25% to 38% with associated durability. Polatuzumab vedotin in combination with BR demonstrated an ORR of 63% with durability. Treatment with CAR T-cell therapy options yield high overall response rates and associated durability ranging from 50-73% and median DORs between 9.2 months and 16.7 months. However, CAR T-cell therapy represents a distinct therapeutic modality and these options may be limited due to eligibility and accessibility reasons. Of the 157 patients with R/R LBCL treated with epcoritamab, 71% had received 3 or more prior lines of systemic therapy, 39% received prior CAR T-cell therapy, 20% with prior autologous stem cell transplant, and 11% with prior polatuzumab vedotin. Therefore, the overall response of 63% with associated durability with epcoritamab provides data to support a clinically meaningful benefit in the context of available therapy for patients with relapsed or refractory large B-cell lymphoma in the 3rd line setting and beyond.

Some limitations of the efficacy data include the following: limited numbers of LBCL subtypes beyond DLBCL, lack of a racially and ethnic diverse population, and limited number of patients with long term exposure to epcoritamab.

Most patients with relapsed or refractory LBCL who were treated with epcoritamab had a diagnosis of DLBCL. While the reclassification of several patients based on MYC, BCL2, and/or BCL6 rearrangement increased the number of patients diagnosed with high-grade B-cell lymphoma (HGBCL), the numbers of patients with primary mediastinal B-cell lymphoma and follicular lymphoma Grade 3B remain very low. Given this and the potential impact on uncertain in efficacy (and safety) in these latter two LBCL subpopulations, the indication was limited to adult patients with relapsed or refractory DLBCL, not otherwise specified, including DLBCL arising from indolent lymphoma, and HGBCL, after two or more lines of systemic therapy.

Additionally, there was limited racial and ethnic representation with no Black or African American or Hispanic or Latino patients. Further characterization of epcoritamab in a broader ethnic and racial population is warranted and informed a postmarketing commitment.

Finally, the proposed treatment regimen is based on treatment data with a median of 5 cycles despite an intended regimen that is administered continuously until disease progression or unacceptable toxicity. The maximum number of cycles a patient received at the time of the initial data cut-off was 20 cycles, but only 31% of the patients had been treated beyond 9 cycles. Although the proposed treatment regimen is supported by durable responses, continued evaluation of the long-term efficacy outcomes remains warranted

8.2. Review of Safety

8.2.1. Safety Review Approach

Data:
The clinical safety evaluation is based on safety data from the GCT3013-01 trial and supported by safety data from the GCT3013-04 trial.
The core safety analysis is based on safety data from the pivotal GCT3013-01 trial, which provides the largest population from a single trial. The GCT3013-01 trial consists of a Dose Escalation Part and an Expansion Part. Data from the Dose Escalation and Expansion Part were pooled for subjects who were assigned to receive the 48 mg dose regimen and received at least one dose of epcoritamab, resulting in an analysis set of 167 subjects with R/R LBCL (the primary safety analysis pool), comprised of 148 subjects with R/R DLBCL and 19 subjects with other aNHL subtypes.
A total of 208 subjects with R/R LBCL were assigned to receive treatment with the 48 mg full dose (167 from GCT3013-01 and 41 from GCT3013-04), which includes the subset of 188 subjects with R/R DLBCL (148 from GCT3013-01 and 40 from GCT3013-04).
Both trials also treated subjects with other R/R B-cell lymphoma subtypes, such as iNHL and MCL. A supportive safety analysis set was created from subjects with all B-NHL subtypes from the pooled GCT3013-01 and GCT3013-04 data. In addition to the 208 LBCL subjects, data was included from 166 subjects with other B-NHL subtypes treated with the 48 mg dosing regimen (128 subjects with iNHL and 38 subjects with MCL), for an overall safety population of 374 subjects (referred to as the "All B-NHL group").

The Applicant's Position:
Overall, the safety analysis strategy is considered adequate to evaluate the safety profile of epcoritamab in R/R LBCL.

The FDA's Assessment:

The FDA conducted safety analyses using the complete datasets provided by the Applicant with a January 31, 2022 data cutoff. The primary safety population consisted of 157 patients with R/R LBCL treated at the RP2D (0.16/0.8/48mg) in the expansion part of Study GCT3013-01. Ten patients with R/R LBCL from the escalation part of Study GCT3013-01 were in the Applicant's primary safety population but not in the FDA primary safety population as these patients, while treated at the RP2D (0.16/0.8/48mg), were not treated at the exact same schedule as those patients in the expansion part. Data from these ten patients were considered supportive and incorporated in the supportive safety population, which was the same as that utilized by the Applicant and consisted of 374 patients with relapsed or refractory aggressive or indolent B-cell Non-Hodgkin Lymphoma (NHL) who were treated with epcoritamab at the RP2D as part of Study GCT3013-01 (n=311) or GCT3013-04 (n=63).

The primary safety population of 157 patients with R/R LBCL supported by an overall supportive safety population of 374 patients with R/R B-cell NHL provided an adequate number of patients for a review of safety.

The FDA clinical review of safety for this BLA is also based on the following:

- Clinical Study Report for study GCT3013-01
- Protocol and statistical analysis plan for study GCT3013-01
- Case report forms and safety narratives
- Summary of clinical safety
- Proposed labeling for epcoritamab

The Applicant reported adverse events using single MedDRA preferred terms (PTs). For increased sensitivity, FDA used a combination of grouped PTs, as defined in Appendix 19.6. Adverse events that involve more than one body system were consolidated and reported under the most commonly involved or most appropriate body system. Unless noted, all presented analyses use the FDA grouped PTs.

8.2.2. Review of the Safety Database

Overall Exposure

Data:

The overall B-NHL population consists of 374 subjects who were assigned to 48 mg epcoritamab and received at least 1 dose of epcoritamab. Safety data from the B-NHL cohort was divided into 5 safety analysis groups as described in Table 41. The 167 subjects in the LBCL group in Trial GCT3013-01 is considered to be the primary safety analysis pool.

Table 41: Applicant –Safety Population, Size, and Denominators

Safety Analysis Group	Studies Included	Patient Population	Number of Subjects
Safety Pool 01	GCT3013-01 (Dose Escalation and Expansion)	LBCL group includes subjects with DLBCL (de novo or transformed), PMBCL, HGBCL, and FL grade 3b **[Primary safety analysis pool][a]**	167 (157 from aNHL expansion cohort and 10 from Dose Escalation Part)
		DLBCL group includes subjects with DLBCL (de novo or transformed)	148 (139 from aNHL expansion cohort and 9 from Dose Escalation Part)
Safety Pool 01+04	GCT3013-01 (Dose Escalation and Expansion GCT3013-04 (Dose Escalation and Expansion)	LBCL group includes subjects with DLBCL (de novo or transformed), PMBCL, HGBCL, and FL grade 3b	208 (157 from GCT3013-01 aNHL expansion cohort, 10 from GCT3013-01 Dose Escalation Part, 36 from GCT3013-04 DLBCL Expansion Part, and 5 from GCT3013-04 dose escalation)
		DLBCL group includes subjects with DLBCL (de novo or transformed)	188 (139 from GCT3013-01 aNHL expansion cohort, 9 from GCT3013-01 Dose Escalation Part, 36 from GCT3013-04 DLBCL Expansion Part, and 4 from GCT3013-04 dose escalation)
		All B-NHL group includes subjects with LBCL, iNHL, and MCL **[Supportive safety analysis pool]**	374 (157 from GCT3013-01 aNHL expansion cohort, 105 from GCT3013-01 iNHL expansion cohort, 37 from GCT3013-01 MCL expansion cohort, 12 from GCT3013-01 Dose Escalation Part, 36 from GCT3013-04 DLBCL Expansion Part, 21 from GCT3013-04 FL Expansion Part, and 6 from GCT3013-04 dose escalation)

Abbreviations: aNHL = aggressive B-cell non-Hodgkin lymphoma; DLBCL = diffuse large B-cell lymphoma; FL = follicular lymphoma; HGBCL = high grade B-cell lymphoma; iNHL = indolent B-cell non-Hodgkin lymphoma; LBCL = large B-cell lymphoma; MCL = mantle cell lymphoma.

[a] population to be used in the draft USPI

Epcoritamab administration and exposure is summarized in Table 42.

Table 42: Applicant – Epcoritamab Exposure (48 mg Safety Analysis Set – Escalation + Expansion)

	Safety Pool 01		Safety Pool 01+04		
	LBCL (N=167)	**DLBCL (N=148)**	**LBCL (N=208)**	**DLBCL (N=188)**	**All B-NHL (N=374)**
Number of Cycles Initiated					
1	167 (100.0%)	148 (100.0%)	208 (100.0%)	188 (100.0%)	374 (100.0%)
2	143 (85.6%)	126 (85.1%)	180 (86.5%)	163 (86.7%)	322 (86.1%)
3	116 (69.5%)	103 (69.6%)	145 (69.7%)	132 (70.2%)	266 (71.1%)
4	99 (59.3%)	88 (59.5%)	124 (59.6%)	113 (60.1%)	220 (58.8%)
5	88 (52.7%)	79 (53.4%)	110 (52.9%)	101 (53.7%)	189 (50.5%)
6	75 (44.9%)	68 (45.9%)	94 (45.2%)	87 (46.3%)	158 (42.2%)
7	69 (41.3%)	63 (42.6%)	86 (41.3%)	80 (42.6%)	143 (38.2%)
8	62 (37.1%)	59 (39.9%)	78 (37.5%)	75 (39.9%)	121 (32.4%)
9	59 (35.3%)	56 (37.8%)	71 (34.1%)	68 (36.2%)	104 (27.8%)
10	53 (31.7%)	51 (34.5%)	61 (29.3%)	59 (31.4%)	87 (23.3%)
11	44 (26.3%)	42 (28.4%)	52 (25.0%)	50 (26.6%)	73 (19.5%)
12	38 (22.8%)	37 (25.0%)	45 (21.6%)	44 (23.4%)	57 (15.2%)
13 [a]	30 (18.0%)	29 (19.6%)	37 (17.8%)	36 (19.1%)	45 (12.0%)
18	4 (2.4%)	4 (2.7%)	4 (1.9%)	4 (2.1%)	5 (1.3%)
N	167	148	208	188	374
Mean (SD)	6.7 (5.37)	6.9 (5.54)	6.6 (5.22)	6.8 (5.34)	6.1 (4.72)
Median	5.0	5.0	5.0	5.0	5.0
Min, Max	1, 22	1, 22	1, 22	1, 22	1, 22
Duration of treatment (months)[b]					
N	167	148	208	188	374
Mean (SD)	5.6 (4.87)	5.8 (5.03)	5.6 (4.73)	5.7 (4.85)	5.1 (4.30)
Median	3.7	3.9	4.2	4.2	3.7
Min, Max	0, 20	0, 20	0, 20	0, 20	0, 20
Number of subjects who received initial intermediate dose, n (%)	**163 (97.6%)**	**144 (97.3%)**	**203 (97.6%)**	**183 (97.3%)**	**362 (96.8%)**
Number of subjects who received initial full dose, n (%)	**156 (93.4%)**	**138 (93.2%)**	**196 (94.2%)**	**177 (94.1%)**	**352 (94.1%)**
Relative Dose Intensity (%) [c]					
Cycle QW [d]					
N	156	138	161	142	296
Median	100.0	100.0	100.0	100.0	100.0
Min, Max	50, 104	50, 104	50, 104	50, 104	37, 104
Cycle Q2W[e]					
N	101	90	104	93	184
Median	100.0	100.0	100.0	100.0	100.0
Min, Max	77, 102	77, 102	77, 102	77, 102	33, 112

	Safety Pool 01		Safety Pool 01+04		
	LBCL (N=167)	**DLBCL (N=148)**	**LBCL (N=208)**	**DLBCL (N=188)**	**All B-NHL (N=374)**
Cycle Q4W[f]					
N	53	51	55	53	76
Median	100.0	100.0	100.0	100.0	100.0
Min, Max	80, 103	80, 103	80, 103	80, 103	80, 105
Number of Subjects experiencing dose delay	**62 (37.1%)**	**52 (35.1%)**	**77 (37.0%)**	**67 (35.6%)**	**152 (40.6%)**
Reason for dose delay [g]					
Adverse Event	46 (27.5%)	38 (25.7%)	60 (28.8%)	52 (27.7%)	124 (33.2%)
Other [h]	20 (12.0%)	17 (11.5%)	21 (10.1%)	18 (9.6%)	42 (11.2%)
Number of subjects with re-priming [i]	**0**	**0**	**1 (0.5%)**	**1 (0.5%)**	**3 (0.8%)**

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

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

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

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

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

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

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

[f] Q4W = Cycles 7+ for -01 ESC; Cycles 10+ for -01 EXP and -04 ESC and EXP

[g] Subjects may experience multiple occurrences of dose delay.

[h] Includes subjects who have dose delay due to COVID-19 control measure (eg, no visits due to quarantine).

[i] Re-priming refers to at least one administration of priming dose after the initial dose of epcoritamab due to extended dose delay.

Data cutoff date:31 Jan 2022

Source: Module 2.7.4 Summary of Clinical Safety Table 2.1.

The Applicant's Position:

Exposure was considered adequate to support the evaluation of safety of the proposed dosing regimen for the target indication. In the Safety Pool 01 LBCL group, median duration of treatment was 3.7 months (range: 0, 20) and median number of cycles of treatment administered per subject was 5.0 (range 1, 22). The majority of subjects (69.5%) received 3 or more cycles of treatment. A total of 99 (59.3%) subjects initiated C4 treatment, providing a conservative estimation of subjects who received 3 months of treatment. Similarly, 69 (41.3%) subjects initiated C7, approximating 6 months of treatment; 59 (31.5%) subjects initiated C10, approximating 9 months of treatment; 30 (18.0%) subjects initiated C13 treatment, approximating 12 months of treatment. There were 53 (31.7%) subjects who continued to

receive epcoritamab treatment as of the data cutoff.

The FDA's Assessment:

The FDA's safety review focused on the 157 patients with R/R LBCL who were treated at the RP2D regimen in the Expansion Part of Study GCT3013-01 (referred to as the primary safety population). Per the proposed dosing regimen, epcoritamab was administered to patients subcutaneously in 28-day cycles, at step-up dosing in Cycle 1 (0.16 mg on Day 1, 0.8 mg on Day 8, and 48 mg on Day 15 and Day 22), 48 mg weekly in Cycles 2-4, 48 mg every other week in Cycles 5-9, and 48 mg every four weeks from Cycles 10 onwards. As summarized in Table 43 , the median exposure duration for patients in the primary safety population was 4.1 months and the median number of cycles initiated was 5. Although epcoritamab was not administered as a fixed duration regimen, the max number of cycles a patient received by the data cut-off of 31 January 2022 was 20 and only 31% of patients were treated beyond 9 cycles, providing limited safety data for epcoritamab exposure for ≥10 cycles.

Overall dose delay occurred in less than half of patients (39%) with the majority of cases due to adverse events. Despite the delays, no patients required re-priming of epcoritamab. Exposure and dose delay were similar in the larger supportive safety population, although 3 patients did require re-priming due to dose delays.

Table 43: FDA Summary of Exposure

			Primary Safety Population N = 157	Supportive Safety Population N = 374
Duration of Treatment				
Exposure duration, months	Median		4.1	3.7
	Range		(0.03-17.9)	(0.03-19.6)
	Q1, Q3		1.2, 9.2	1.4, 8.1
Relative dose intensity (%)	Q1W[a]	n	147	296
		Median	100	100
		Range	(50-104)	(37-104)
	Q2W[a]	n	94	184
		Median	100	100
		Range	(77-102)	(33-112)
	Q4W[a]	n	49	76
		Median	100	100
		Range	(80-103)	(80-105)
Treatment cycles	Median		5	5
	Min		1	1
	Max		20	22
Number of Cycles, n (%)	≤5		86 (55)	216 (58)
	6-10		31 (20)	85 (23)
	11-15		28 (18)	52 (14)
	>15		12 (8)	21 (6)
Dose Delays and Re-Priming				
Dose Delay[b], n (%)	≥1 dose delay		62 (39)	152 (41)
	Due to AE		46 (29)	124 (33)
	Due to "other"[c]		20 (13)	42 (11)
Re-priming[d], n (%)			0	3 (0.8)

Abbreviations: AE: adverse event
[a] Q1W: weekly dosing Cycles 1-4, Q2W: every other week Cycles 5-9, Q4W: every 4 weeks Cycles ≥10
[b] Patients may experience multiple occurrences of dose delay
[c] Includes patients who have dose delay due to COVID-19 control measures (quarantine)
[d] Re-priming refers to at least one administration of priming dose after initial epcoritamab due to extended dose delay
Source: FDA analysis

Relevant characteristics of the safety population:

Data:
Demographic characteristics are summarized by safety analysis group in Table 44.

Table 44: Applicant – Summary of Demographic Characteristics (48 mg Safety Analysis Set – Escalation + Expansion)

	Safety Pool 01		Safety Pool 01+04		
	LBCL (N=167)	DLBCL (N=148)	LBCL N=208	DLBCL N=188	All B-NHL N=374
Age at informed consent (years)					
n	167	148	208	188	374
Mean (SD)	62.3 (13.76)	64.0 (12.42)	63.3 (13.19)	64.8 (11.86)	64.4 (12.24)
Median	65.0	66.5	66.0	67.5	66.5
Min, Max	20, 83	22, 83	20, 89	22, 89	20, 89
<65 years, n (%)	83 (49.7%)	68 (45.9%)	96 (46.2%)	80 (42.6%)	157 (42.0%)
65 to <75 years, n (%)	53 (31.7%)	49 (33.1%)	73 (35.1%)	69 (36.7%)	144 (38.5%)
≥75 years, n (%)	31 (18.6%)	31 (20.9%)	39 (18.8%)	39 (20.7%)	73 (19.5%)
Sex (at birth), n (%)					
Male	104 (62.3%)	94 (63.5%)	125 (60.1%)	114 (60.6%)	231 (61.8%)
Female	63 (37.7%)	54 (36.5%)	83 (39.9%)	74 (39.4%)	143 (38.2%)
Race, n (%)					
White	106 (63.5%)	93 (62.8%)	106 (51.0%)	93 (49.5%)	207 (55.3%)
Asian	30 (18.0%)	27 (18.2%)	71 (34.1%)	67 (35.6%)	111 (29.7%)
Other	7 (4.2%)	5 (3.4%)	7 (3.4%)	5 (2.7%)	12 (3.2%)
Not Reported	24 (14.4%)	23 (15.5%)	24 (11.5%)	23 (12.2%)	44 (11.8%)
Ethnicity, n (%)					
Hispanic or Latino	2 (1.2%)	1 (0.7%)	2 (1.0%)	1 (0.5%)	4 (1.1%)
Not Hispanic or Latino	32 (19.2%)	29 (19.6%)	73 (35.1%)	69 (36.7%)	120 (32.1%)
Not Reported	133 (79.6%)	118 (79.7%)	133 (63.9%)	118 (62.8%)	250 (66.8%)
Region, n (%)					
North America	25 (15.0%)	22 (14.9%)	25 (12.0%)	22 (11.7%)	53 (14.2%)
Europe	93 (55.7%)	82 (55.4%)	93 (44.7%)	82 (43.6%)	180 (48.1%)
Asia	27 (16.2%)	25 (16.9%)	68 (32.7%)	65 (34.6%)	106 (28.3%)
Other	22 (13.2%)	19 (12.8%)	22 (10.6%)	19 (10.1%)	35 (9.4%)
Weight (kg) at Baseline					
n	167	148	208	188	374
Mean (SD)	74.1 (16.72)	73.8 (16.50)	70.8 (17.13)	70.3 (16.96)	72.9 (17.55)
Median	72.0	72.0	69.0	69.0	70.2
Min, Max	39, 144	39, 144	39, 144	39, 144	39, 144
<55 kg, n (%)	16 (9.6%)	13 (8.8%)	38 (18.3%)	35 (18.6%)	57 (15.2%)

	Safety Pool 01		Safety Pool 01+04		
	LBCL (N=167)	DLBCL (N=148)	LBCL N=208	DLBCL N=188	All B-NHL N=374
55-<65 kg, n (%)	38 (22.8%)	37 (25.0%)	47 (22.6%)	45 (23.9%)	78 (20.9%)
65-<85 kg, n (%)	69 (41.3%)	60 (40.5%)	78 (37.5%)	69 (36.7%)	149 (39.8%)
≥85 kg, n (%)	44 (26.3%)	38 (25.7%)	45 (21.6%)	39 (20.7%)	90 (24.1%)
ECOG Performance Status, n (%)					
0	80 (47.9%)	72 (48.6%)	103 (49.5%)	95 (50.5%)	196 (52.4%)
1	82 (49.1%)	71 (48.0%)	98 (47.1%)	86 (45.7%)	162 (43.3%)
2	5 (3.0%)	5 (3.4%)	7 (3.4%)	7 (3.7%)	16 (4.3%)
Baseline renal function (CrCl mL/min), n (%)					
Normal (≥90)	70 (41.9%)	60 (40.5%)	77 (37.0%)	67 (35.6%)	135 (36.1%)
Mildly impaired (60 - <90)	69 (41.3%)	65 (43.9%)	90 (43.3%)	86 (45.7%)	161 (43.0%)
Moderately impaired (30 - <60)	25 (15.0%)	21 (14.2%)	38 (18.3%)	33 (17.6%)	72 (19.3%)
Severe impaired (15 - <30)	0	0	0	0	0
Missing	3 (1.8%)	2 (1.4%)	3 (1.4%)	2 (1.1%)	6 (1.6%)
Baseline hepatic function per NCI criteria, n (%)					
Normal	132 (79.0%)	118 (79.7%)	168 (80.8%)	154 (81.9%)	309 (82.6%)
Mild dysfunction	30 (18.0%)	26 (17.6%)	35 (16.8%)	30 (16.0%)	58 (15.5%)
Moderate dysfunction	1 (0.6%)	1 (0.7%)	1 (0.5%)	1 (0.5%)	1 (0.3%)
Severe dysfunction	0	0	0	0	0
Unknown	1 (0.6%)	1 (0.7%)	1 (0.5%)	1 (0.5%)	1 (0.3%)
Missing	3 (1.8%)	2 (1.4%)	3 (1.4%)	2 (1.1%)	5 (1.3%)

Abbreviations: B-NHL = B-cell non-Hodgkin lymphoma; DLBCL= diffuse large B-cell lymphoma; iNHL = indolent non-Hodgkin lymphoma; LBCL= large B-cell lymphoma; MCL = mantle cell lymphoma; SD = standard deviation.
Note: Safety Pool 01 includes GCT3013-01. Safety Pool 01+04 includes GCT3013-01 and GCT3013-04. All B-NHL is comprised of the LBCL population plus subjects with iNHL (n=128) and MCL (n=38) from the escalation and expansion parts of the trials.
Percentages calculated based on N. Ethnicity is only collected for subjects enrolled in United States.
Note: Baseline renal function calculated based on estimated creatine clearance using the Cockcroft Gault method.
Data cutoff date:31 Jan 2022
Source: Module 2.7.4 Summary of Clinical Safety Table 1.2

Baseline disease characteristics are summarized by safety analysis group in Table 45.

Table 45: Applicant – Summary of Baseline Disease Characteristics (48 mg Safety Analysis Set – Escalation + Expansion)

	Safety Pool 01		Safety Pool 01+04		
	LBCL (N=167)	DLBCL (N=148)	LBCL N=208	DLBCL N=188	All B-NHL N=374
Disease Type at Study Entry, n (%)					
DLBCL	148 (88.6%)	148 (100.0%)	188 (90.4%)	188 (100.0%)	188 (50.3%)
Other subtype of LBCL	19 (11.4%)	0	20 (9.6%)	0	20 (5.3%)
FL[a]	0	0	0	0	115 (30.7%)
Other subtype of iNHL	0	0	0	0	13 (3.5%)
MCL	0	0	0	0	38 (10.2%)
Time from initial diagnosis to 1st dose[b] (years)					

	Safety Pool 01		Safety Pool 01+04		
	LBCL (N=167)	DLBCL (N=148)	LBCL N=208	DLBCL N=188	All B-NHL N=374
N	167	148	208	188	374
Mean (SD)	3.1 (4.24)	3.2 (4.44)	3.3 (4.35)	3.4 (4.52)	5.4 (5.84)
Median	1.6	1.6	1.7	1.7	3.0
Min, Max	0.0, 28.4	0.0, 28.4	0.0, 28.4	0.0, 28.4	0.0, 35.0
Ann Arbor Staging, n (%)					
Stage I	6 (3.6%)	5 (3.4%)	8 (3.8%)	7 (3.7%)	10 (2.7%)
Stage IE	1 (0.6%)	1 (0.7%)	1 (0.5%)	1 (0.5%)	2 (0.5%)
Stage II	29 (17.4%)	26 (17.6%)	35 (16.8%)	32 (17.0%)	49 (13.1%)
Stage IIE	6 (3.6%)	6 (4.1%)	6 (2.9%)	6 (3.2%)	6 (1.6%)
Stage III	20 (12.0%)	17 (11.5%)	30 (14.4%)	27 (14.4%)	66 (17.6%)
Stage IIIE	1 (0.6%)	1 (0.7%)	2 (1.0%)	2 (1.1%)	4 (1.1%)
Stage IIIS	1 (0.6%)	1 (0.7%)	1 (0.5%)	1 (0.5%)	4 (1.1%)
Stage IIIE, S	0	0	0	0	0
Stage IV	103 (61.7%)	91 (61.5%)	125 (60.1%)	112 (59.6%)	233 (62.3%)
IPI, n (%)					
0-2	NA	60 (40.5%)	NA	75 (39.9%)	75 (20.1%)
≥3	NA	86 (58.1%)	NA	111 (59.0%)	111 (29.7%)
Unknown	NA	2 (1.4%)	NA	2 (1.1%)	2 (0.5%)
Not Applicable	NA	0	NA	0	186 (49.7%)
Presence of Constitutional Symptoms, n (%)					
Any Constitutional Symptom	25 (15.0%)	21 (14.2%)	28 (13.5%)	23 (12.2%)	49 (13.1%)
Night Sweats	16 (9.6%)	13 (8.8%)	17 (8.2%)	14 (7.4%)	35 (9.4%)
Weight Loss (>10% over last 6 mo)	4 (2.4%)	4 (2.7%)	5 (2.4%)	5 (2.7%)	11 (2.9%)
Fever	7 (4.2%)	6 (4.1%)	8 (3.8%)	6 (3.2%)	9 (2.4%)
Extreme Fatigue	6 (3.6%)	6 (4.1%)	6 (2.9%)	6 (3.2%)	12 (3.2%)
Number of prior lines of anti-lymphoma therapy					
1, n (%)	2 (1.2%)	2 (1.4%)	2 (1.0%)	2 (1.1%)	3 (0.8%)
2, n (%)	48 (28.7%)	43 (29.1%)	65 (31.3%)	59 (31.4%)	113 (30.2%)
3, n (%)	50 (29.9%)	47 (31.8%)	60 (28.8%)	57 (30.3%)	106 (28.3%)
≥4, n (%)	67 (40.1%)	56 (37.8%)	81 (38.9%)	70 (37.2%)	152 (40.6%)
Time from end of last-line anti-lymphoma therapy to 1st dose (months)					
n	167	148	208	188	374
Mean (SD)	6.2 (14.21)	6.4 (15.02)	6.4 (13.53)	6.6 (14.16)	8.8 (16.23)
Median	2.6	2.6	2.6	2.6	3.1
Min, Max	0, 153	0, 153	0, 153	0, 153	0, 153
Prior CAR-T	65 (38.9%)	56 (37.8%)	67 (32.2%)	58 (30.9%)	83 (22.2%)
Time from end of last CAR-T therapy to 1st dose (months)					
n	65	56	67	58	83
Mean (SD)	7.7 (6.01)	7.8 (6.39)	7.7 (5.92)	7.8 (6.28)	8.9 (8.47)
Median	5.5	5.3	5.6	5.4	6.2
Min, Max	2, 31	2, 31	2, 31	2, 31	2, 56
Prior ASCT, n (%)	33 (19.8%)	28 (18.9%)	41 (19.7%)	36 (19.1%)	71 (19.0%)

	Safety Pool 01		Safety Pool 01+04		
	LBCL (N=167)	DLBCL (N=148)	LBCL N=208	DLBCL N=188	All B-NHL N=374
Time from end of last anti-CD-20 containing therapy to 1st dose (months)					
n	167	148	208	188	374
Mean (SD)	9.8 (16.44)	10.3 (17.33)	9.9 (15.57)	10.3 (16.24)	15.3 (22.08)
Median	5.1	5.4	5.0	5.1	6.6
Min, Max	1, 153	1, 153	0, 153	0, 153	0, 153

Abbreviations: ASCT = autologous stem-cell transplantation; B-NHL = B-cell non-Hodgkin lymphoma; CAR-T = chimeric antigen receptor T-cell; DLBCL= diffuse large B-cell lymphoma; FL = follicular lymphoma; iNHL = indolent non-Hodgkin lymphoma; LBCL= large B-cell lymphoma; MCL = mantle cell lymphoma; NA = Not applicable; SD = standard deviation.
Note: Safety Pool 01 includes GCT3013-01. Safety Pool 01+04 includes GCT3013-01 and GCT3013-04. All B-NHL is comprised of the LBCL population plus subjects with iNHL (n=128) and MCL (n=38) from the escalation and expansion parts of the trials.
Percentages calculated based on N.

[a] Includes all FL subjects from -01 esc since histologic grade was not collected for this portion of the study, includes only FL grade 1-3a from -01 exp and -04 study, as FL grade 3b is included within LBCL.

[b] Time from diagnosis of disease recorded at time of study entry.

Data cutoff date:31 Jan 2022
Source: Module 2.7.4 Summary of Clinical Safety Table 1.3

The Applicant's Position:

Key baseline characteristics and prior treatment history of subjects in Safety Pool 01 reflect a broad, elderly, heavily pre-treated, and highly refractory population that is clinically challenging to treat, with historically poor responses and survival outcomes.

The FDA's Assessment:

The patient characteristics for patients in the primary and supportive safety populations are shown in the Table 46 below. In the 157 patients included in the primary safety population, the median age was 64, 60% were male, and over half the patients were White (61%). The majority of patients in the primary safety population had an ECOG status of 0-1 with few patients having an ECOG status of 2.

Most patients were enrolled from ex-US sites with only 15% of those in the primary safety population being enrolled in the U.S. Additionally, there was limited representation regarding race and ethnicity with no Black or African American or Hispanic or Latino patients included in the primary safety population. Inclusion of an overall diverse population was also not present when examining the demographics of the larger supportive safety population.

Table 46: FDA Summary of Patient Demographics in the Primary and Supportive Safety Populations

Characteristic	Primary Safety Population N = 157	Supportive Safety Population N = 374
Age		
Median	64	66.5
Range	(20, 83)	(20, 89)
≥65 to <75, n (%)	48 (31)	144 (39)
≥75, n (%)	29 (18)	73 (20)
Sex, n (%)		
Male	94 (60)	231 (62)
Female	63 (40)	143 (38)
Race, n (%)		
White	96 (61)	207 (55)
Black	0	0
Asian	30 (19)	111 (30)
Native Hawaiian or Pacific Islander	1 (0.6)	1 (0.3)
American Indian or Alaska Native	0	1 (0.3)
Other	6 (4)	10 (3)
Not Reported	24 (15)	44 (12)
Ethnicity, n (%)		
Hispanic	0	4 (1)
Non-Hispanic	24 (15)	120 (32)
Not reported	133 (85)	250 (67)
Country, n (%)		
US	24 (15)	50 (13)
Non-US	133 (85)	324 (87)
Australia	22 (14)	35 (9)
Canada	1 (0.6)	3 (0.8)
Denmark	10 (6)	26 (7)
France	23 (15)	41 (11)
Germany	5 (3)	13 (3)
Italy	3 (2)	8 (2)
Japan	0	63 (17)
Korea	21 (13)	36 (10)
Netherlands	14 (9)	28 (7)
Poland	6 (4)	13 (3)
Singapore	6 (4)	7 (2)
Spain	10 (6)	26 (7)
Sweden	0	1 (0.3)

Characteristic	Primary Safety Population N = 157	Supportive Safety Population N = 374
United Kingdom	12 (8)	24 (6)
ECOG PS, n (%)		
0	74 (47)	196 (52)
1	78 (50)	162 (43)
2	5 (3)	16 (4)

Abbreviations: US, United States; ECOG PS Eastern Cooperative Oncology Group Performance Status
Source: FDA Analysis

The disease and treatment characteristics for patients in both the primary and supportive safety populations are shown in Table 47 below. Analysis focused on the primary safety population, which consisted of patients with R/R LBCL consistent with the proposed indication. Among the 157 patients in the primary safety population, the majority had DLBCL (89%) and advanced stage disease (Stage III/IV: 75%). The population was overall heavily pretreated with a median of 3 lines of prior therapy and 39% of patients treated with at least 4 or more. Over half of the patients (61%) were considered to have primary refractory disease and 39% and 20% of patients had had prior CAR-T therapy or autologous stem cell transplant, respectively.

Table 47: FDA Summary of Baseline Disease and Prior Treatment Characteristics of the Primary and Supportive Safety Populations

Disease Characteristic		Primary Safety Population N = 157	Supportive Safety Population N = 374
Diagnosis[a] n (%)	DLBCL	139 (89)	188 (50)
	FL Grade 3B	5 (3)	5 (1)
	HGBCL	9 (6)	10 (3)
	PMBCL	4 (3)	5 (1)
	MCL	0	38 (10)
	Indolent lymphoma[b]	0	128 (34)
Stage n (%)	I	6 (4)	12 (3)
	II	33 (21)	55 (15)
	III	21 (13)	74 (20)
	IV	97 (62)	233 (62)
Prior Lines of Therapy	Median	3	3
	Range	2-11	1-11
	1, n (%)	0	3 (0.8)
	2, n (%)	46 (29)	113 (30)
	3, n (%)	50 (32)	106 (28)

Disease Characteristic		Primary Safety Population N = 157	Supportive Safety Population N = 374
	≥4, n (%)	61 (39)	152 (41)
Primary refractory disease		96 (61)	201 (54)
Prior therapy	Anti-CD20± alkylating agent	157 (100)	374 (100)
	Anthracyclines	154 (98)	331 (89)
	Anti-CD19	7 (4)	11 (3)
	Polatuzumab	17 (11)	20 (5)
	CAR-T	61 (39)	87 (23)
	ASCT	31 (20)	71 (19)

Abbreviations: DLBCL, diffuse large B cell lymphoma; high-grade B-cell lymphoma; PMBCL, primary mediastinal B-cell lymphoma; FL, follicular lymphoma; MCL; mantle cell lymphoma; ASCT, autologous stem cell transplant; CAR-T, chimeric antigen T cell therapy

[a] Diagnosis provided at entry prior to subset of 88 patients with DLBCL further tested by FISH

[b] Subtypes of indolent lymphoma represented: FL Grades 1-3a, marginal zone lymphoma, small lymphocytic leukemia

Source: FDA Analysis

Adequacy of the safety database:

Data:

An integrated safety database was created to support the integrated safety analyses described in this application.

The evaluation of safety is based on the primary safety analysis pool comprising 167 subjects with LBCL from the pivotal GCT3013-01 trial, supplemented with safety data from the GCT3013-04 trial. All subjects in the safety analysis pool were assigned to receive the 48 mg full dose and received at least 1 dose of epcoritamab. The data cutoff date was 31 Jan 2022.

The Applicant's Position:

The safety database is considered adequate to evaluate the safety of epcoritamab in patients with R/R LBCL after 2 or more lines of systemic therapy.

The FDA's Assessment:

The size of the integrated safety database, denoted in the FDA analyses as the supportive safety population, of 374 patients with relapsed/refractory B-cell NHL who received epcoritamab

monotherapy at the full dose of 48 mg and the size of the primary safety data base of 157 patients with relapsed/refractory LBCL who received epcoritamab monotherapy at the RP2D regimen are considered adequate for review.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

Data:
The clinical sites were monitored following standard operating procedures. Data were queried per study-specific data management plans. Individual case safety reports were followed up as necessary to obtain complete information on the case. SAEs were reconciled between the clinical and safety databases. No meaningful data integrity concerns were reported from site audits.

The Applicant's Position:
No issues were identified regarding data integrity or submission quality that had an effect on the safety review.

The FDA's Assessment:
The FDA agrees with the Applicant's position. The quality of the safety data submitted was adequate for substantive review. The Applicant provided full datasets for patients enrolled in Study GCT3013-01 and GCT3013-04.

Categorization of Adverse Event

Data:
N/A

The Applicant's Position:
All AE summaries are based on TEAEs. A TEAE is defined as a newly occurring or worsening AE during the on-treatment period (treatment-emergent):

- GCT3013-01 Dose Escalation Part: from the day of first dose of trial medication to 28 days after last dose of trial medication, or initiation of new anti-lymphoma therapy, whichever came first
- GCT3013-01 expansion part + GCT3013-04 dose escalation and expansion parts: from the day of first dose of trial medication to 60 days after last dose of trial medication, or initiation of new anti-lymphoma therapy, whichever came first.

TEAEs were coded to standard PT and SOC using the Medical Dictionary for Regulatory

Activities (MedDRA, Version 24.1 for all studies). TEAE severity grades were based on the NCI CTCAE version 5.0. The AESIs of CRS, ICANS, and CTLS were graded as follows: CRS and ICANS were graded according to ASTCT criteria (Lee et al, 2019) and CTLS by Cairo-Bishop criteria (Coiffier et al, 2008) across all of these studies, except for ICANS-like neurological symptoms in the Dose Escalation Part of GCT3013-01 (graded by CTCAE v5.0).
Unless specified otherwise, subjects are counted at most once at the PT level, and at most once at the SOC level, even if subjects had multiple episodes of the same event or multiple PTs within the same SOC.

The FDA's Assessment:
The FDA agrees with the Applicant's position. All adverse events and serious adverse events were captured during the trial and for up to 60 days after the last dose of study treatment or until the initiation of another systemic anti-cancer therapy, whichever occurred first. The FDA's review of safety is focused on treatment emergent adverse events (TEAE) that occurred within 30 days of the last dose of study treatment. Given the single-arm trial design and the absence of a comparator arm, FDA considers all TEAEs regardless of attribution in the assessment of safety.

Routine Clinical Tests

Data:
N/A

The Applicant's Position:
For laboratory tests with toxicity grades defined by the CTCAE 5.0, the following laboratory tests were analyzed for on-treatment laboratory evaluation by treatment-emergent worst CTCAE grade and shift tables (baseline and worst CTCAE grade):

- Hematology and coagulation:
    - Hematology: hemoglobin (hypo), absolute neutrophils count (ANC) (hypo), absolute lymphocytes count (hyper and hypo), platelets (hypo), INR, aPTT
- Serum Chemistry and Electrolytes:
    - Serum Chemistry: ALT (hyper), albumin (hypo), AST (hyper), ALP (hyper), bicarbonate (hypo), calcium (hyper and hypo), creatinine (hyper), glucose (hypo), LDH (hyper), magnesium (hyper and hypo), sodium (hypo), potassium (hyper and hypo), total bilirubin (hyper), uric acid (elevated)

The FDA's Assessment:
The FDA agrees with the Applicant's position.

8.2.4. Safety Results

Deaths

Data:

In the Safety Pool 01 LBCL group, fatal TEAEs were reported for 12 (7.2%) subjects. Nine of the deaths occurred during the Expansion Part and 3 of the deaths occurred during Dose Escalation Part. One fatal TEAE of ICANS was considered related to epcoritamab by the investigator; all other TEAEs were not considered related to epcoritamab by the investigator or sponsor. Fatal TEAEs attributed to disease progression (6 subjects), included general physical health deterioration (2 subjects), loss of consciousness due to cerebral hemorrhage, pulmonary embolism, hepatotoxicity, and malignant neoplasm progression. Fatal TEAEs related to COVID-19 infection (3 subjects), included COVID-19 (2 subjects) and COVID 19 pneumonia. Fatal TEAEs attributed to existing comorbidities/impact of prior therapies (2 subjects) included myocardial infarction (1 subject, existing cardiac disease) and PML (1 subject, attributed to prior rituximab exposure).

Eleven of the 12 fatal TEAEs were on treatment events with onset during the first 2 cycles of treatment, except for the event of loss of consciousness due to cerebral hemorrhage (in the setting of progressive disease), which occurred beyond first 2 cycles

Deaths occurring for any reason are summarized by safety analysis group in Table 48.

Table 48: Applicant – Summary of Deaths (48 mg Safety Analysis Set – Escalation + Expansion)

Number of Subjects, n (%)	Safety Pool 01[a]		Safety Pool 01+04[a]		
	Primary LBCL (N=167)	DLBCL (N=148)	LBCL (N=208)	DLBCL (N=188)	Supportive All B-NHL (N=374)
Deaths	**68 (40.7%)**	**62 (41.9%)**	**83 (39.9%)**	**76 (40.4%)**	**102 (27.3%)**
Primary cause of death					
Disease progression	54 (32.3%)	49 (32.9%)	69 (33.2%)	63 (33.5%)	78 (20.9%)
Adverse event[b]	7 (4.2%)	7 (4.7%)	7 (3.4%)	7 (3.7%)	15 (4.0%)
Other	6 (3.6%)[c]	5 (3.4%)	6 (2.9%)	5 (2.7%)	8 (2.1%)
Unknown	1 (0.6%)	1 (0.7%)	1 (0.5%)	1 (0.5%)	1 (0.3%)
Deaths within 60 days of last dose[e]	**37 (22.2%)**	**33 (22.3%)**	**42 (20.2%)**	**37 (19.7%)**	**56 (15.0%)**
Primary cause of death					
Disease progression	30 (18.0%)	26 (17.6%)	35 (16.8%)	30 (16.0%)	40 (10.7%)
Adverse event	5 (3.0%)	5 (3.4%)	5 (2.4%)	5 (2.7%)	13 (3.5%)
Other	2 (1.2%)[d]	2 (1.4%)	2 (1.0%)	2 (1.1%)	3 (0.8%)
Unknown	0	0	0	0	0

Abbreviations: DLBCL= diffuse large B-cell lymphoma; iNHL = indolent non-Hodgkin lymphoma; LBCL= large B-cell lymphoma; MCL = mantle cell lymphoma; TEAE = treatment-emergent adverse event.

[a] Safety Pool 01 includes GCT3013-01. Safety Pool 01+04 includes GCT3013-01 and GCT3013-04. All B-NHL is comprised of the LBCL population plus subjects with iNHL (n=128) and MCL (n=38) from the Dose Escalation and Expansion Parts of the trials.

[b] Primary cause of death due to adverse event (n=15); not all subjects with fatal TEAEs (n=19 in Table 7) had adverse event listed as a primary cause of death.
[c] Other (n=7) deaths were due to: PD; AML (second malignancy); multiorgan failure due to sepsis following initiation of new anti-lymphoma therapy; systemic infection; loss of consciousness due to cerebral hemorrhage (related to PD); septic shock; hypoxic respiratory failure following transplant.
[d] Other (n=2) deaths were due to: PD; loss of consciousness due to cerebral hemorrhage (related to PD)
[e] 60 days from last dose or 28 days from last dose for GCT3013-01 Dose Escalation Part [uncensored for start of subsequent anti-lymphoma treatment]

Data cutoff date: 31 Jan 2022
Source: Module 2.7.4 Summary of Clinical Safety Table 3.1.2 and Listing 3.17

The Applicant's Position:

Overall, most deaths were due to disease progression.

The FDA's Assessment:

Treatment emergent deaths were assessed up to 60 days post treatment discontinuation. For safety, the FDA considers all-cause treatment emergent adverse events in the evaluation versus those indicated as treatment-related by the Applicant. The FDA concurs that as of the 31 January 2022 data cutoff, a total of 68 deaths occurred within the Applicant's primary LBCL population (n=167) with most of the deaths attributed to progression of disease. As depicted in Table 49, 61 deaths were counted as part of the FDA assessment of the primary safety population (n=157). Similar to the Applicant analysis, the majority of deaths were due to progressive disease. For 7 patients, death was attributed to an adverse event, which included 2 cases of COVID-19 and 1 case each of hepatotoxicity, pulmonary embolism, progressive multifocal leukoencephalopathy, ICANS, and myocardial infarction. Notably, the patient who developed Grade 5 hepatotoxicity had lymphoma involvement of the liver at screening and developed Grade 3 hepatotoxicity on Day 14 of treatment with progression to Grade 5 on Day 21.

Table 49: FDA Summary of Deaths in Primary and Supportive Safety Populations

	Primary Safety Population N=157	Supportive Safety Population N=374
Deaths	61 (39)	102 (27)
Cause of Death		
Disease Progression	50 (32)	80 (21)[a]
Adverse Event	7 (4)	15 (4)
Other[b]	4 (3)	7 (2)

[a] 1 death initially counted as unknown but narrative designated as due to progressive disease, 1 death counted as other but due to disease progression while on treatment with epcoritamab.
[b] Other deaths: Primary population: 1 death due to septic shock in setting of disease progression and NALT, 1 death due to systemic infection following disease progression, 1 death due to neurological decline following disease progression, 1 death due to COVID-19 following NALT; Supportive population: 4 same deaths as in primary and additional 3 deaths; 1 case due to multiorgan failure in setting of sepsis following NALT; 1 case due to progressive acute myeloid leukemia which occurred after disease progression; 1 case died due to complications from transplant;
Source: FDA Analysis

The 4-month Safety Update provided safety data collected through 30 June 2022. Three additional fatal treatment-emergent adverse events occurred in the Applicant's primary safety population (n=167). All 3 fatal adverse events were related to infection with 2 due to COVID-19 pneumonia and 1 due to COVID-19. The Applicant noted that these three deaths were not treatment-related. However, each patient was recently on therapy with epcoritamab prior to development of COVID-19, which may have contributed to the severity of the COVID-19 in each patient.

- Patient (b) (6): Last dose of epcoritamab was Day 239 (Cycle 9) and start day of COVID-19 pneumonia was Day 255. Death occurred on Day 269.
- Patient (b) (6): Last dose of epcoritamab was Day 486 (Cycle 18) and start day of COVID-19 pneumonia was Day 497. Death occurred on Day 562.
- Patient (b) (6): Last dose of epcoritamab was Day 589 (Cycle 22) and start day of COVID-19 was Day 591. Death occurred on Day 624.

An additional 19 patients were noted to have fatal adverse events in the supportive safety population at the time of the 4-month Safety Update. Excluding the three deaths discussed above, 8 patient deaths were due to COVID-19 pneumonia, 2 patient deaths due to COVID-19, 1 patient death due multiorgan failure secondary to CRS, 1 patient death due to ICANS, 2 patient deaths due to septic shock, 1 patient death due to progressive disease, and 1 patient death due to cardiopulmonary failure which occurred after an acute myocardial infarction. Of note, the patients who experienced fatal ICANS, CRS, and septic shock all had MCL. Based on the available data, patients with MCL appear to have a higher risk of severe, serious, or fatal events due to the known toxicities with epcoritamab including CRS, ICANS, and infection. The risk in

patients with MCL raises concerns regarding increased toxicity, although an understanding of the underlying mechanism for the increased risk remains unclear at this time. Continued prospective evaluation of patients with MCL with adequate safety monitoring and management for known risks is warranted.

Overall, most deaths are due to progressive disease with a low number due to adverse events.

Serious Adverse Events

Data:
Serious TEAEs that occurred in ≥2% of subjects in any group are summarized by safety analysis group in Table 50.

Table 50: Applicant – Serious Treatment-Emergent Adverse Events in ≥2% of Subjects in any Group by SOC and PT (48 mg Safety Analysis Set – Escalation + Expansion)

System Organ Class Preferred Term, n (%)	Safety Pool 01[a]		Safety Pool 01+04[a]		
	Primary LBCL (N=167)	DLBCL (N=148)	LBCL (N=208)	DLBCL (N=188)	Supportive All B-NHL (N=374)
Subjects with at ≥1 serious TEAE	**97 (58.1%)**	**87 (58.8%)**	**113 (54.3%)**	**102 (54.3%)**	**151 (40.4%)**
Immune system disorders	**52 (31.1%)**	**45 (30.4%)**	**60 (28.8%)**	**52 (27.7%)**	**131 (35.0%)**
Cytokine release syndrome	52 (31.1%)	45 (30.4%)	60 (28.8%)	52 (27.7%)	131 (35.0%)
Infections and infestations	**27 (16.2%)**	**24 (16.2%)**	**33 (15.9%)**	**30 (16.0%)**	**15 (4.0%)**
Pneumonia	4 (2.4%)	4 (2.7%)	5 (2.4%)	5 (2.7%)	3 (0.8%)
Sepsis	4 (2.4%)	4 (2.7%)	4 (1.9%)	4 (2.1%)	2 (0.5%)
COVID-19	3 (1.8%)	3 (2.0%)	3 (1.4%)	3 (1.6%)	1 (0.3%)
Nervous system disorders	**11 (6.6%)**	**11 (7.4%)**	**13 (6.3%)**	**12 (6.4%)**	**13 (3.5%)**
ICANS	4 (2.4%)	4 (2.7%)	5 (2.4%)	5 (2.7%)	9 (2.4%)
Respiratory, thoracic and mediastinal disorders	**12 (7.2%)**	**9 (6.1%)**	**12 (5.8%)**	**9 (4.8%)**	**2 (0.5%)**
Pleural effusion	8 (4.8%)	5 (3.4%)	8 (3.8%)	5 (2.7%)	2 (0.5%)
General disorders and administration site conditions	**9 (5.4%)**	**9 (6.1%)**	**9 (4.3%)**	**9 (4.8%)**	**4 (1.1%)**
Pyrexia	4 (2.4%)	4 (2.7%)	4 (1.9%)	4 (2.1%)	1 (0.3%)
Blood and lymphatic system disorders	**8 (4.8%)**	**8 (5.4%)**	**8 (3.8%)**	**8 (4.3%)**	**3 (0.8%)**
Febrile neutropenia	4 (2.4%)	4 (2.7%)	4 (1.9%)	4 (2.1%)	1 (0.3%)

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

Note: Adverse events were classified using MedDRA v24.1 and CTCAE v5.0 and were counted only once per category. CRS and ICANS were graded according to (Lee et al., 2019) and CTLS was graded according to Cairo-Bishop (Coiffier et al, 2008).

[a] Safety Pool 01 includes GCT3013-01. Safety Pool 01+04 includes GCT3013-01 and GCT3013-04. All B-NHL is comprised of the LBCL population plus subjects with iNHL (n=128) and MCL (n=38) from the Dose Escalation and Expansion Parts of the trials.

Data cutoff date: 31 Jan 2022

Source: Module 2.7.4 Summary of Clinical Safety Table 3.13

The Applicant's Position:

The incidence and type of serious TEAEs are consistent with that expected for R/R LBCL subjects treated with a bispecific CD3/CD20-directed T-cell engager and is considered manageable with appropriate monitoring and mitigation measures.

The FDA's Assessment:

The FDA independently performed an analysis of all treatment-emergent serious adverse events (SAEs) that occurred in both the primary and supportive safety populations. Table 51 summarizes this analysis, depicting the total number of SAEs and lists the most common SAEs which occurred in ≥2% of patients by SOC and PT. The FDA's analysis showed that SAEs occurred in 57% (89/157) of patients in the Primary Safety Population with the most common being CRS (29%), sepsis (6%), pleural effusion (5%), COVID-19 (3%), febrile neutropenia (3%), fever (3%), ICANS (3%), renal insufficiency (3%), and urinary tract infection (3%). Findings were similar for SAEs in the supportive safety population, although CRS was noted to be of higher incidence likely owing to the inclusion of MCL patients. As noted in the section above, patients with MCL appear to have a higher risk of severe, serious, or fatal events due to the known toxicities with epcoritamab including CRS, ICANS, and infection. The risk in patients with MCL raises concerns regarding increased toxicity, although an understanding of the underlying mechanism for the increased risk remains unclear at this time. Continued prospective evaluation of patients with MCL with adequate safety monitoring and management for known risks is warranted.

Overall, the FDA analysis was consistent with the Applicant's findings with the most common treatment-emergent SAEs similar to those observed with other bispecific CD3/CD20-directed T-cell engagers. Differences between the FDA analysis and the Applicant's were due to the FDA's use of FDA grouped preferred terms, a slightly smaller and more specific primary safety population, and inclusion of adverse events regardless of attribution. The FDA does not agree with the Applicant's determination of "relatedness" of treatment-emergent adverse events to epcoritamab. In a single arm trial, FDA considers all treatment-emergent events in analyses because it is not possible to clearly distinguish between adverse events related to the underlying disease versus adverse events that are due to the toxicity of study treatment.

Table 51: FDA Summary of Serious Adverse Events in ≥2% of Patients

MedDRA System Organ Class FDA Grouped Preferred Term (PT) or MedDRA PT	Primary Safety Population N=157 n, (%)	Supportive Safety Population N=374 n, (%)
Any SAE	89 (57)	218 (58)
Immune System Disorders		
CRS (by ASTCT)	46 (29)	131 (35)
Infections and Infestations		
Sepsis	9 (6)	14 (4)
COVID-19	5 (3)	14 (4)
Urinary tract infection	4 (3)	10 (2)
Cellulitis	3 (2)	3 (0.8)
Pneumonia	3 (2)	16 (4)
Upper Respiratory Tract Infection	3 (2)	6 (2)
Herpesvirus infection	2 (1)	7 (2)
Respiratory, Thoracic, and Mediastinal Disorders		
Pleural Effusion	7 (5)	11 (3)
Blood and Lymphatic System Disorders		
Febrile Neutropenia	4 (3)	5 (1)
General Disorders and Administration Site Conditions		
Fever	4 (3)	10 (3)
Nervous System Disorders		
ICANS	4 (3)	9 (2)
Neurological changes	3 (2)	4 (1)
Renal and Urinary Disorders		
Renal Insufficiency	4 (3)	7 (2)
Neoplasms Benign, Malignant, and Unspecified		
Second Primary Malignancy	2 (1)	6 (2)

Abbreviations: SAE, serious adverse event,;CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome
Source: FDA Analysis

Dropouts and/or Discontinuations Due to Adverse Effects

Data:

TEAEs leading to permanent treatment discontinuation in ≥2% of subjects in any group are summarized by safety analysis set in Table 52. Treatment-related TEAEs leading to treatment

discontinuation included a CRS (grade 1), ICANS (grade 5), and worsening of pre-existing CLIPPERS (grade 3) in 1 (0.6%) subject each

Table 52: Applicant – TEAEs Leading Treatment Discontinuation Reported for ≥2% of Subjects in Any Group by SOC and PT (48 mg Safety Analysis Set – Escalation + Expansion)

System Organ Class Preferred Term, n (%)	Safety Pool 01[a]		Safety Pool 01+04[a]		
	Primary LBCL (N=167)	DLBCL (N=148)	LBCL (N=208)	DLBCL (N=188)	Supportive All B-NHL (N=374)
Subjects with at ≥1 TEAE leading to dose discontinuation	**13 (7.8%)**	**12 (8.1%)**	**15 (7.2%)**	**14 (7.4%)**	**24 (6.4%)**
Infections and infestations	**5 (3.0%)**	**5 (3.4%)**	**5 (2.4%)**	**5 (2.7%)**	**9 (2.4%)**
COVID-19	2 (1.2%)	2 (1.4%)	2 (1.0%)	2 (1.1%)	2 (0.5%)
COVID-19 pneumonia	2 (1.2%)	2 (1.4%)	2 (1.0%)	2 (1.1%)	3 (0.8%)
Progressive multifocal leukoencephalopathy	1 (0.6%)	1 (0.7%)	1 (0.5%)	1 (0.5%)	1 (0.3%)
Pneumonia	0	0	0	0	1 (0.3%)
Sepsis	0	0	0	0	1 (0.3%)
Septic shock	0	0	0	0	1 (0.3%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**3 (1.8%)**	**3 (2.0%)**	**5 (2.4%)**	**5 (2.7%)**	**6 (1.6%)**
Myelodysplastic syndrome	2 (1.2%)	2 (1.4%)	2 (1.0%)	2 (1.1%)	2 (0.5%)
Chronic myelomonocytic leukaemia	0	0	1 (0.5%)	1 (0.5%)	1 (0.3%)
Lung neoplasm	1 (0.6%)	1 (0.7%)	1 (0.5%)	1 (0.5%)	1 (0.3%)
Pancreatic carcinoma	0	0	1 (0.5%)	1 (0.5%)	1 (0.3%)
Angioimmunoblastic T-cell lymphoma	0	0	0	0	1 (0.3%)
General disorders and administration site conditions	**2 (1.2%)**	**2 (1.4%)**	**2 (1.0%)**	**2 (1.1%)**	**3 (0.8%)**
Fatigue	1 (0.6%)	1 (0.7%)	1 (0.5%)	1 (0.5%)	1 (0.3%)
General physical health deterioration	1 (0.6%)	1 (0.7%)	1 (0.5%)	1 (0.5%)	1 (0.3%)
Multiple organ dysfunction syndrome	0	0	0	0	1 (0.3%)
Nervous system disorders	**2 (1.2%)**	**2 (1.4%)**	**2 (1.0%)**	**2 (1.1%)**	**2 (0.5%)**
Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids	1 (0.6%)	1 (0.7%)	1 (0.5%)	1 (0.5%)	1 (0.3%)
Immune effector cell-associated neurotoxicity syndrome	1 (0.6%)	1 (0.7%)	1 (0.5%)	1 (0.5%)	1 (0.3%)
Immune system disorders	**1 (0.6%)**	**1 (0.7%)**	**1 (0.5%)**	**1 (0.5%)**	**2 (0.5%)**
Cytokine release syndrome	1 (0.6%)	1 (0.7%)	1 (0.5%)	1 (0.5%)	2 (0.5%)
Respiratory, thoracic and mediastinal disorders	**1 (0.6%)**	**0**	**1 (0.5%)**	**0**	**2 (0.5%)**
Pleural effusion	1 (0.6%)	0	1 (0.5%)	0	1 (0.3%)
Dyspnoea	0	0	1 (0.5%)	0	1 (0.3%)
Ear and labyrinth disorders	**0**	**0**	**0**	**0**	**1 (0.3%)**
Deafness	0	0	0	0	1 (0.3%)

System Organ Class Preferred Term, n (%)	Safety Pool 01[a]		Safety Pool 01+04[a]		
	Primary LBCL (N=167)	DLBCL (N=148)	LBCL (N=208)	DLBCL (N=188)	Supportive All B-NHL (N=374)
Gastrointestinal disorders	**0**	**0**	**0**	**0**	**2 (0.5%)**
Diarrhoea	0	0	0	0	1 (0.3%)
Enteritis	0	0	0	0	1 (0.3%)

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

Note: Adverse events were classified using MedDRA v24.1 and CTCAE v5.0 and were counted only once per category.

[a] Safety Pool 01 includes GCT3013-01. Safety Pool 01+04 includes GCT3013-01 and GCT3013-04. All B-NHL is comprised of the LBCL population plus subjects with iNHL (n=128) and MCL (n=38) from the Dose Escalation and Expansion Parts of the trials.

Data cutoff date: 31 Jan 2022

Source: Module 2.7.4 Summary of Clinical Safety Table 3.10

The Applicant's Position:

Thirteen (7.8%) subjects in the Safety Pool 01 LBCL group discontinued treatment due to an adverse event. TEAEs leading to treatment discontinuation reported for more than 1 subject included COVID-19, COVID-19 pneumonia, and MDS: 2 (1.2%) subjects each. Most TEAEs leading to treatment discontinuation were not treatment-related.

The FDA's Assessment:

FDA performed an analysis of TEAEs leading to the discontinuation of epcoritamab in both the primary and supportive safety populations, which is summarized in Table 53. In general, the FDA agrees with the Applicant's summary of all-cause adverse events leading to treatment discontinuation. The FDA analysis is similar to that of the Applicant's with the overall treatment discontinuation due to adverse events occurring in 8% (12/157) and 6% (24/374) of patients within the primary and supportive safety populations, respectively. Small differences in incidence were likely due to the use FDA grouped preferred terms as well as the slightly smaller and more specific primary safety population. For safety, the FDA considers all-cause treatment emergent adverse events in the evaluation versus those indicated as treatment-related. Based on this approach, the most common adverse events leading to discontinuation in both safety populations were COVID-19 and second primary malignancies, each affecting 2% (3/157) in the primary safety population and 1% (5/374) in the supportive safety population. Of note, the malignancies listed in this category mainly affected 1 patient each except for myelodysplastic syndrome, which occurred in 2 patients.

Table 53: FDA Summary of Adverse Events Leading to Treatment Discontinuation

MedDRA System Organ Class FDA Grouped Preferred Term (PT) or MedDRA PT	Primary Safety Population N=157 n, (%)	Supportive Safety Population N=374 n, (%)
Patients who discontinued treatment due to AE	12 (8)	24 (6)
Infection and Infestations		
COVID-19	3 (2)	5 (1)
PML	1 (0.6)	1 (0.3)
Sepsis	0	3 (0.8)
Pneumonia	0	1 (0.3)
Neoplasms, Benign, Malignant, and Unspecified		
Second Primary Malignancy[a]	3 (2)	5 (1)
Nervous System Disorders		
CLIPPERS	1 (0.6)	1 (0.3)
ICANS	1 (0.6)	1 (0.3)
Neurological Changes	0	1 (0.3)
Immune System Disorders		
CRS	1 (0.6)	2 (0.5)
Respiratory, Thoracic, Mediastinal Disorders		
Pleural Effusion	1 (0.6)	1 (0.3)
Dyspnea	0	1 (0.3)
General Disorders and Administration Site Conditions		
Fatigue[b]	1 (0.6)	1 (0.3)
General Physical Health Deterioration	1 (0.6)	1 (0.3)
Multiorgan Dysfunction Syndrome	0	1 (0.3)
Gastrointestinal Disorders		
Diarrhea	0	1 (0.3)
Gastroenteritis	0	1 (0.3)

Abbreviations: AE, adverse event; PML: progressive multifocal leukoencephalopathy; CLIPPERS, Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids; ICANS, Immune effector cell-associated neurotoxicity syndrome

[a] Second Primary malignancies: Primary population: 2 cases of myelodysplastic syndrome, 1 case of "lung neoplasm;" Supportive population: 2 cases of myelodysplastic syndrome, 1 case of chronic myelomonocytic leukemia, 1 case of "lung neoplasm," 1 case of pancreatic cancer, 1 case of angioimmunoblastic T-cell lymphoma

[b] Fatigue co-occurred with CRS in the same patient and noted that treatment discontinued for both AEs.

Source: FDA Analysis

Dose Interruption/Reduction Due to Adverse Effects

Data:

TEAEs leading to dose delay in ≥2% of subjects in any group are summarized by safety analysis set in Table 54.

Table 54: Applicant – TEAEs Leading to Dose Delay Reported for ≥2% of Subjects in Any Group by SOC and PT (48 mg Safety Analysis Set – Escalation + Expansion)

System Organ Class Preferred Term, n (%)	Safety Pool 01[a]		Safety Pool 01+04[a]		
	Primary LBCL (N=167)	DLBCL (N=148)	LBCL (N=208)	DLBCL (N=188)	Supportive All B-NHL (N=374)
Subjects with at ≥1 TEAE leading to dose delay	**60 (35.9%)**	**51 (34.5%)**	**76 (36.5%)**	**67 (35.6%)**	**151 (40.4%)**
Infections and infestations	**22 (13.2%)**	**20 (13.5%)**	**28 (13.5%)**	**26 (13.8%)**	**63 (16.8%)**
Urinary tract infection	2 (1.2%)	2 (1.4%)	4 (1.9%)	4 (2.1%)	7 (1.9%)
COVID-19	3 (1.8%)	3 (2.0%)	3 (1.4%)	3 (1.6%)	10 (2.7%)
Immune system disorders	**12 (7.2%)**	**8 (5.4%)**	**15 (7.2%)**	**11 (5.9%)**	**29 (7.8%)**
Cytokine release syndrome	12 (7.2%)	8 (5.4%)	15 (7.2%)	11 (5.9%)	29 (7.8%)
Blood and lymphatic system disorders	**12 (7.2%)**	**12 (8.1%)**	**13 (6.3%)**	**13 (6.9%)**	**29 (7.8%)**
Neutropenia	7 (4.2%)	7 (4.7%)	8 (3.8%)	8 (4.3%)	16 (4.3%)
Thrombocytopenia	4 (2.4%)	4 (2.7%)	4 (1.9%)	4 (2.1%)	10 (2.7%)
Investigations	**5 (3.0%)**	**4 (2.7%)**	**12 (5.8%)**	**11 (5.9%)**	**22 (5.9%)**
Neutrophil count decreased	0	0	4 (1.9%)	4 (2.1%)	5 (1.3%)
General disorders and administration site conditions	**6 (3.6%)**	**6 (4.1%)**	**6 (2.9%)**	**6 (3.2%)**	**20 (5.3%)**
Pyrexia	5 (3.0%)	5 (3.4%)	5 (2.4%)	5 (2.7%)	10 (2.7%)
Nervous system disorders	**6 (3.6%)**	**6 (4.1%)**	**6 (2.9%)**	**6 (3.2%)**	**13 (3.5%)**
Immune effector cell-associated neurotoxicity syndrome	3 (1.8%)	3 (2.0%)	3 (1.4%)	3 (1.6%)	5 (1.3%)
Respiratory, thoracic and mediastinal disorders	**6 (3.6%)**	**5 (3.4%)**	**6 (2.9%)**	**5 (2.7%)**	**11 (2.9%)**
Pleural effusion	4 (2.4%)	3 (2.0%)	4 (1.9%)	3 (1.6%)	4 (1.1%)
Renal and urinary disorders	**4 (2.4%)**	**1 (0.7%)**	**5 (2.4%)**	**2 (1.1%)**	**6 (1.6%)**
Acute kidney injury	4 (2.4%)	1 (0.7%)	4 (1.9%)	1 (0.5%)	5 (1.3%)

Abbreviations: : B-NHL = B-cell non-Hodgkin lymphoma; COVID-19 = coronavirus disease 2019; CRS = cytokine release syndrome; CTCAE = Common Terminology Criteria for Adverse Events; DLBCL= diffuse large B-cell lymphoma; ICANS = immune effector cell-associated neurotoxicity syndrome; iNHL = indolent non-Hodgkin lymphoma; LBCL= large B-cell lymphoma; MCL = mantle cell lymphoma; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.

Note: Adverse events were classified using MedDRA v24.1 and CTCAE v5.0 and were counted only once per category. CRS and ICANS were graded according to (Lee et al., 2019) and CTLS was graded according to Cairo-Bishop (Coiffier et al, 2008).

[a] Safety Pool 01 includes GCT3013-01. Safety Pool 01+04 includes GCT3013-01 and GCT3013-04. All B-NHL is comprised of the LBCL population plus subjects with iNHL (n=128) and MCL (n=38) from the Dose Escalation and Expansion Parts of the trials.

Data cutoff date: 31 Jan 2022

Source: Module 2.7.4 Summary of Clinical Safety Table 3.9

The Applicant's Position:

In the Safety Pool 01 LBCL group, 60 (35.9%) subjects experienced at least 1 TEAE leading to dose delay. Overall, the safety profile of epcoritamab was managed by preventative measures, dose delays when indicated, supportive care measures, and appropriate monitoring. These steps contributed to a manageable safety profile for epcoritamab in the monotherapy setting.

The FDA's Assessment:

The FDA analysis of the adverse events resulting in treatment interruption or delay of epcoritamab is shown in Table 55 and is consistent with the trends observed by the Applicant's analysis. Thirty-four percent (54/157) of patients in the primary safety population and 40% (151/374) of patients in the supportive safety population experienced an adverse event that was associated with a dose delay or interruption, most often due to infection, CRS, or neutropenia. The FDA notes that dose delays were the primary method of management of adverse events rather than discontinuation of treatment.

Table 55: FDA Summary of Adverse Events Leading to Dose Interruption

MedDRA System Organ Class FDA Grouped Preferred Term (PT) or MedDRA PT	Primary Safety Population N=157 n, (%)	Supportive Safety Population N=374 n, (%)
Patients with treatment delay due to AE	54 (34)	151 (40)
Immune System Disorders		
CRS	11 (7)	29 (8)
Blood and Lymphatic System Disorders		
Neutropenia	7 (4)	21 (6)
Thrombocytopenia	5 (3)	13 (3)
Infections and Infestations		
Sepsis	6 (4)	8 (2)
Urinary Tract Infection	4 (3)	10 (3)
Upper Respiratory Infection	3 (2)	8 (2)
Pneumonia	0	12 (3)
COVID-19	2 (1)	11 (3)
Herpesvirus infection	1 (0.6)	8 (2)
General Disorders and Administration Site Conditions		
Fever	4 (3)	10 (3)
Fatigue	2 (1)	7 (2)
Neurologic Disorders		
ICANS	3 (2)	5 (1)
Respiratory, Thoracic, Mediastinal Disorders		
Pleural Effusion	4 (3)	4 (1)
Renal and Urinary Disorders		
Renal Insufficiency	3 (2)	6 (2)

Abbreviations: AE, adverse event; ICANS, Immune effector cell-associated neurotoxicity syndrome
Source: FDA Analysis

Significant Adverse Events

Data:
The most common grade 3 or 4 TEAEs (≥5%), regardless of causality, are summarized by safety analysis set in Table 56.

Table 56: Applicant – Grade 3 or 4 TEAEs Reported in ≥5% of Subjects in Any Group (48 mg Safety Analysis Set – Escalation + Expansion)

System Organ Class Preferred Term, n (%)	Safety Pool 01[a]		Safety Pool 01+04[a]		
	Primary LBCL (N=167)	DLBCL (N=148)	LBCL (N=208)	DLBCL (N=188)	Supportive All B-NHL (N=374)
Subjects with ≥1 grade 3 or 4 TEAE	**100 (59.9%)**	**89 (60.1%)**	**136 (65.4%)**	**124 (66.0%)**	**239 (63.9%)**
Blood and lymphatic system disorders	**46 (27.5%)**	**42 (28.4%)**	**53 (25.5%)**	**49 (26.1%)**	**97 (25.9%)**
Neutropenia	26 (15.6%)	25 (16.9%)	27 (13.0%)	26 (13.8%)	52 (13.9%)
Anaemia	17 (10.2%)	17 (11.5%)	22 (10.6%)	22 (11.7%)	32 (8.6%)
Thrombocytopenia	10 (6.0%)	9 (6.1%)	11 (5.3%)	10 (5.3%)	20 (5.3%)
Investigations	**22 (13.2%)**	**19 (12.8%)**	**47 (22.6%)**	**44 (23.4%)**	**83 (22.2%)**
Neutrophil count decreased	10 (6.0%)	7 (4.7%)	25 (12.0%)	22 (11.7%)	37 (9.9%)
Lymphocyte count decreased	4 (2.4%)	4 (2.7%)	15 (7.2%)	15 (8.0%)	24 (6.4%)

Abbreviations: AESI = adverse event of special interest; B-NHL = B-cell non-Hodgkin lymphoma; CRS = cytokine release syndrome; CTCAE = Common Terminology Criteria for Adverse Events; CTLS = clinical tumor lysis syndrome; DLBCL= diffuse large B-cell lymphoma; ICANS = immune effector cell-associated neurotoxicity syndrome; iNHL = indolent non-Hodgkin lymphoma; LBCL= large B-cell lymphoma; MCL = mantle cell lymphoma; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.

Note: Adverse events were classified using MedDRA v24.1 and CTCAE v5.0 and were counted only once per category. CRS and ICANS were graded according to (Lee et al., 2019) and CTLS was graded according to Cairo-Bishop (Coiffier et al, 2008).

[a] Safety Pool 01 includes GCT3013-01. Safety Pool 01+04 includes GCT3013-01 and GCT3013-04. All B-NHL is comprised of the LBCL population plus subjects with iNHL (n=128) and MCL (n=38) from the Dose Escalation and Expansion Parts of the trials.

Data cutoff date: 31 Jan 2022

Source: Module 2.7.4 Summary of Clinical Safety Table 3.11

The Applicant's Position:

The safety profile of epcoritamab, including the incidence of Grade 3 or 4 TEAEs, is generally consistent with that expected for R/R LBCL subjects treated with a bispecific CD3/CD20-directed T-cell engager and is considered manageable with appropriate monitoring and mitigation measures.

The FDA's Assessment:

The FDA analysis of grade 3 or 4 treatment-emergent adverse events observed in the primary and supportive safety populations is displayed in Table 57. The FDA concurs with the general findings shown by the Applicant and with the position that these adverse events have been observed with other bispecific CD3/CD20-directed T-cell engagers. However, there are notable differences due to FDA's use of grouped preferred terms rather than a single preferred term. Specifically, the most common (≥5%) grade 3 or 4 adverse events include sepsis, lymphopenia, and leukopenia in addition to neutropenia, anemia, and thrombocytopenia. The incidences of neutropenia and thrombocytopenia are also significantly increased.

Of note, the USPI will include the incidences of laboratory abnormalities based on the laboratory dataset as adverse event reporting may underestimate the incidence.

Table 57: FDA Summary of Grade 3 or 4 Treatment-emergent Adverse Events Occurring in ≥5% of Patients

MedDRA System Organ Class FDA Grouped Preferred Term (PT) or MedDRA PT	Primary Safety Population N=157 n, (%)	Supportive Safety Population N=374 n, (%)
Any Grade 3 or 4 AE	93 (59)	239 (64)
Blood and Lymphatic System Disorders		
Neutropenia	33 (21)	88 (24)
Anemia	16 (10)	32 (9)
Thrombocytopenia	14 (9)	36 (10)
Lymphopenia	8 (5)	34 (9)
Leukopenia	5 (3)	19 (5)
Infections and Infestations		
Sepsis	9 (6)	15 (4)

Abbreviations: AE, adverse event
Source: FDA Analysis

Treatment Emergent Adverse Events and Adverse Reactions

Data:
An overview of TEAEs by safety analysis set is provided in Table 58. The most common TEAEs (≥10%) by safety analysis set is provided in Table 59.
TEAEs were also analyzed over time from initial epcoritamab administration for the following time periods: Week ≤8, Week 8 to ≤12, Week 12 to ≤36, and Week 36+. Interpretation of these data require consideration of the length of the time and dosing schedules during each time period chosen for analysis. In the Safety Pool 01 LBCL group, the highest incidences of TEAEs over time generally occurred during the first 2 cycles of treatment with epcoritamab (Week ≤8).

Table 58: Applicant – Overview of TEAEs (48 mg Safety Analysis Set – Escalation + Expansion)

Number of Subjects, n (%)	Safety Pool 01[a]		Safety Pool 01+04[a]		
	Primary LBCL (N=167)	DLBCL (N=148)	LBCL (N=208)	DLBCL (N=188)	Supportive All B-NHL (N=374)
Number of Subjects with at ≥1:					
TEAE	166 (99.4%)	147 (99.3%)	207 (99.5%)	187 (99.5%)	368 (98.4%)
Related TEAE	140 (83.8%)	124 (83.8%)	181 (87.0%)	164 (87.2%)	332 (88.8%)
Grade 3 and higher TEAE	105 (62.9%)	94 (63.5%)	141 (67.8%)	129 (68.6%)	248 (66.3%)
Grade 3 and higher related TEAE	47 (28.1%)	42 (28.4%)	79 (38.0%)	73 (38.8%)	145 (38.8%)

Number of Subjects, n (%)	Safety Pool 01[a]		Safety Pool 01+04[a]		
	Primary LBCL (N=167)	DLBCL (N=148)	LBCL (N=208)	DLBCL (N=188)	Supportive All B-NHL (N=374)
TEAE by worst toxicity grade					
1	20 (12.0%)	18 (12.2%)	21 (10.1%)	19 (10.1%)	34 (9.1%)
2	41 (24.6%)	35 (23.6%)	45 (21.6%)	39 (20.7%)	86 (23.0%)
3	62 (37.1%)	56 (37.8%)	79 (38.0%)	73 (38.8%)	144 (38.5%)
4	31 (18.6%)	27 (18.2%)	50 (24.0%)	45 (23.9%)	85 (22.7%)
5	12 (7.2%)	11 (7.4%)	12 (5.8%)	11 (5.9%)	19 (5.1%)
Serious TEAE	97 (58.1%)	87 (58.8%)	113 (54.3%)	102 (54.3%)	218 (58.3%)
Serious related TEAE	61 (36.5%)	54 (36.5%)	74 (35.6%)	66 (35.1%)	151 (40.4%)
TEAE leading to treatment discontinuation	13 (7.8%)	12 (8.1%)	15 (7.2%)	14 (7.4%)	24 (6.4%)
TEAE leading to dose delay	60 (35.9%)	51 (34.5%)	76 (36.5%)	67 (35.6%)	151 (40.4%)
Fatal TEAE[b]	12 (7.2%)	11 (7.4%)	12 (5.8%)	11 (5.9%)	19 (5.1%)
Fatal related TEAE	1 (0.6%)	1 (0.7%)	1 (0.5%)	1 (0.5%)	1 (0.3%)

Abbreviations: B-NHL = B-cell non-Hodgkin lymphoma; = CTCAE = Common Terminology Criteria for Adverse Events; CTLS = clinical tumor lysis syndrome; DLBCL= diffuse large B-cell lymphoma; iNHL = indolent non-Hodgkin lymphoma; LBCL= large B-cell lymphoma; MCL = mantle cell lymphoma; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.

Note: Adverse events were classified using MedDRA v24.1 and CTCAE v5.0 and were counted only once per category. CRS and ICANS were graded according to (Lee et al., 2019) and CTLS was graded according to Cairo-Bishop (Coiffier et al, 2008).

[a] Safety Pool 01 includes GCT3013-01. Safety Pool 01+04 includes GCT3013-01 and GCT3013-04. All B-NHL is comprised of the LBCL population plus subjects with iNHL (n=128) and MCL (n=38) from the Dose Escalation and Expansion Parts of the trials.

[b] Four of the subjects in B-NHL group reported in this row (4, 3, 4, and 3 of the subjects in each column, respectively) were also reported by investigator with primary cause of death as disease progression.

Data cutoff date: 31 Jan 2022

Source: Module 2.7.4 Summary of Clinical Safety Table 3.1.

Table 59: Applicant – Treatment-Emergent Adverse Events in at Least 10% of Subjects in Any Group (48 mg Safety Analysis Set – Escalation and Expansion)

Preferred Term, n (%)	Safety Pool 01[a]		Safety Pool 01+04[a]		
	Primary LBCL (N=167)	DLBCL (N=148)	LBCL (N=208)	DLBCL (N=188)	Supportive All B-NHL (N=374)
Subjects with ≥1 TEAE	**166 (99.4%)**	**147 (99.3%)**	**207 (99.5%)**	**187 (99.5%)**	**368 (98.4%)**
Cytokine release syndrome	84 (50.3%)	73 (49.3%)	119 (57.2%)	107 (56.9%)	230 (61.5%)
Injection site reaction	37 (22.2%)	35 (23.6%)	59 (28.4%)	57 (30.3%)	116 (31.0%)
Nausea	34 (20.4%)	32 (21.6%)	43 (20.7%)	40 (21.3%)	66 (17.6%)
Pyrexia	38 (22.8%)	33 (22.3%)	42 (20.2%)	37 (19.7%)	82 (21.9%)

Preferred Term, n (%)	Safety Pool 01[a]		Safety Pool 01+04[a]		
	Primary LBCL (N=167)	DLBCL (N=148)	LBCL (N=208)	DLBCL (N=188)	Supportive All B-NHL (N=374)
Fatigue	41 (24.6%)	38 (25.7%)	41 (19.7%)	38 (20.2%)	85 (22.7%)
Diarrhoea	33 (19.8%)	30 (20.3%)	38 (18.3%)	35 (18.6%)	69 (18.4%)
Neutropenia	37 (22.2%)	35 (23.6%)	38 (18.3%)	36 (19.1%)	68 (18.2%)
Anaemia	30 (18.0%)	28 (18.9%)	37 (17.8%)	35 (18.6%)	56 (15.0%)
Decreased appetite	19 (11.4%)	18 (12.2%)	28 (13.5%)	27 (14.4%)	41 (11.0%)
Constipation	20 (12.0%)	18 (12.2%)	26 (12.5%)	24 (12.8%)	49 (13.1%)
Hypokalaemia	14 (8.4%)	14 (9.5%)	26 (12.5%)	26 (13.8%)	37 (9.9%)
Abdominal pain	23 (13.8%)	21 (14.2%)	25 (12.0%)	23 (12.2%)	35 (9.4%)
Neutrophil count decreased	10 (6.0%)	7 (4.7%)	25 (12.0%)	22 (11.7%)	40 (10.7%)
Headache	21 (12.6%)	17 (11.5%)	24 (11.5%)	20 (10.6%)	47 (12.6%)
Vomiting	20 (12.0%)	19 (12.8%)	24 (11.5%)	23 (12.2%)	34 (9.1%)
Thrombocytopenia	22 (13.2%)	21 (14.2%)	23 (11.1%)	22 (11.7%)	35 (9.4%)
Insomnia	18 (10.8%)	16 (10.8%)	22 (10.6%)	19 (10.1%)	39 (10.4%)
Back pain	18 (10.8%)	15 (10.1%)	21 (10.1%)	18 (9.6%)	32 (8.6%)
Injection site erythema	14 (8.4%)	14 (9.5%)	20 (9.6%)	20 (10.6%)	34 (9.1%)
Oedema peripheral	19 (11.4%)	18 (12.2%)	19 (9.1%)	18 (9.6%)	33 (8.8%)

Abbreviations: CRS = cytokine release syndrome; CTCAE = Common Terminology Criteria for Adverse Events; CTLS = clinical tumor lysis syndrome; DLBCL= diffuse large B-cell lymphoma; ICANS = immune effector cell-associated neurotoxicity syndrome; iNHL = indolent non-Hodgkin lymphoma; LBCL= large B-cell lymphoma; MCL = mantle cell lymphoma; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.

Note: Adverse events were classified using MedDRA v24.1 and CTCAE v5.0 and were counted only once per category. CRS and ICANS were graded according to (Lee et al., 2019) and CTLS was graded according to Cairo-Bishop (Coiffier et al, 2008).

[a] Safety Pool 01 includes GCT3013-01. Safety Pool 01+04 includes GCT3013-01 and GCT3013-04. The B-NHL group is comprised of the LBCL population plus subjects with iNHL (n=128) and MCL (n=38) from the Dose Escalation and Expansion Parts of the trials.

Data cutoff date: 31 Jan 2022

Source: Module 2.7.4 Summary of Clinical Safety Table 3.3

The Applicant's Position:

The TEAEs observed with the 48 mg full dose of epcoritamab were generally consistent with those expected for a bispecific CD3/CD20-directed T-cell engager. The most common (≥10%) TEAEs included CRS (84 subjects; 50.3%); fatigue (41 subjects; 24.6%); pyrexia (38 subjects; 22.8%); injection site reaction and neutropenia (37 subjects; 22.2% each); nausea (34 subjects; 20.4%), diarrhea (33 subjects; 19.8%); anemia (30 subjects; 18.0%); abdominal pain (23 subjects; 13.8%); thrombocytopenia (22 subjects; 13.2%); headache (21 subjects; 12.6%); constipation and vomiting (20 subjects; 12.0% each); decreased appetite and edema peripheral (19 subjects; 11.4% each); and back pain and insomnia (18 subjects; 10.8%).

The FDA's Assessment:

Treatment emergent adverse events were assessed from the start of study drug until 30 days after the last study drug administration. In the primary safety population, any grade TEAEs were

reported in 99%. The FDA analysis of TEAEs (>5%) using FDA grouped preferred terms is displayed in the Table 60 in decreasing order of incidence by system organ class and preferred term. The most common TEAEs (excluding laboratory abnormalities) in the primary safety population (≥20%) were CRS (51%; 80/157), fatigue (29%; 45/157), administration related reactions (28%; 44/157), musculoskeletal pain (28%, 44/157), neutropenia (28%, 44/157), fever (24%; 37/157), abdominal pain (23%; 36/157), diarrhea (20%; 32/157), and nausea (20%; 31/157). Findings were similar in the supportive safety population. For laboratory abnormalities, see the Laboratory Findings section below.

Of note, for adverse reactions, the FDA disagrees with the Applicant's definition. Given the single-arm trial design of GCT3013-01, FDA considers all TEAEs as an adverse drug reaction unless unequivocally due to the underlying disease or an extraneous cause. For the epcoritamab prescribing information (USPI), the adverse reactions included are based on the FDA definition.

Table 60: FDA Summary of Treatment-emergent Adverse Events Occurring in ≥10% of Patients

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MedDRA System Organ Class FDA Grouped Preferred Term (PT) or MedDRA PT	Primary Safety Population N=157 n, (%)	Supportive Safety Population N=374 n, (%)
Any Grade AE	156 (99)	268 (98)
Immune System Disorders		
CRS[b]	80 (51)	230 (61)
General Disorders and Administration Site Conditions		
Fatigue	45 (29)	105 (28)
Fever	37 (24)	82 (22)
Edema	22 (14)	47 (13)
Injury, Poisoning, and Procedural Complications		
Administration Related Reaction	44 (28)	151 (40)
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal pain	44 (28)	90 (24)
Blood and Lymphatic System Disorders		
Neutropenia	44 (28)	106 (28)
Anemia	28 (18)	56 (15)
Thrombocytopenia	24 (15)	60 (16)
Lymphopenia	10 (6)	39 (10)
Gastrointestinal Disorders		
Abdominal pain	36 (23)	57 (15)
Diarrhea	32 (20)	69 (18)
Nausea	31 (20)	66 (18)
Constipation	20 (13)	49 (13)
Vomiting	19 (12)	34 (9)
Skin and Subcutaneous Tissue disorders		
Rash	23 (15)	80 (21)
Nervous System Disorders		
Headache	21 (13)	47 (13)
Peripheral neuropathy and paresthesia	15 (10)	30 (8)
Neurological changes	15 (10)	37 (10)
Metabolism and Nutrition Disorders		
Decreased Appetite	19 (12)	41 (11)
Cardiac Disorders		
Cardiac arrhythmias	16 (10)	26 (7)
Psychiatric Disorders		
Insomnia	15 (10)	39 (10)
Respiratory, Thoracic, and Mediastinal Disorders		
Cough	14 (9)	37 (10)

Abbreviations: AE, adverse event; CRS, cytokine release syndrome
[a] Ordering based on incidence in primary population
[b] Includes 2 additional cases noted in ADCRS Dataset, all other AEs based on ADAE dataset
Source: FDA Analysis

Laboratory Findings

Data:
Hematology:
In the Safety Pool 01 LBCL group, the following worsening CTCAE grades from baseline were observed:

- ANC (hypo) (N=158): 48.7% of subjects had a worsening of ≥1 grade, including 17.7% to grade 3 and 13.3% to grade 4
- Platelets (hypo) (N=163): 49.1% had a worsening of ≥1 grade, including 6.1% to grade 3 and 6.7% to grade 4
- Hemoglobin (hypo) (N=163): 62.0% of subjects had a worsening of ≥1 grade, including 12.9% to grade 3 and none to grade 4
- Lymphocytes (hypo) (N=156): 87.2% of subjects had a worsening of ≥1 grade, including 37.8% to grade 3 and 40.4% to grade 4

Biochemistry:
In the Safety Pool 01 LBCL group, the following worsening in CTCAE grades from baseline based on elevations in LFTs were observed:

- ALT (N=162): 44.4% of subjects had a worsening of ≥1 grade, including 4.9% to grade 3 and none to grade 4
- AST (N=161): 46.0% of subjects had a worsening of ≥1 grade, including to 3.7% grade 3 and 0.6% to grade 4
- ALP (N=162): 31.5% of subjects had a worsening of ≥1 grade, including to 1.2% grade 3 and none to grade 4
- Total bilirubin (N=162): 13.6% of subjects had a worsening of ≥1 grade, including 2.5% to grade 3 and 0.6% to grade 4

The most frequently observed grade 3 or 4 electrolyte abnormality was hypokalemia with shifts in 7 (4.3%) of 162 subjects to grade 3 and 1 (0.6%) subject to grade 4. Grade 3 or 4 abnormalities were observed for ≤4.9% of subjects across groups for all other biochemistry analytes.
Drug-Induced Liver Abnormalities:
In the Safety Pool 01 LBCL group (N=167), 5 (3.0%) subjects had AST/ALT >3×ULN and total bilirubin >2×ULN within 30 days of the first dose. Four out of the 5 subjects did not meet Hy's Law criteria due to concurrent ALP elevation >2 x ULN. Out of the 5 subjects, 4 (2.4%) subjects had LFT elevations within 1 day of epcoritamab administration. In 3 subjects, the LFT elevations occurred in the context of progressive disease, with reported causes of death being either disease progression (n=2) or hepatotoxicity due to disease progression (n=1). In the other

2 subjects, the LFT elevations were transient and resolved along with concurrent TEAEs of CRS (n=1) or liver injury (n=1). The hepatotoxicity and liver injury were not considered related to epcoritamab by the investigator. Both subjects continued treatment and were ongoing as of the data cutoff date.

The Applicant's Position:

Exposure to epcoritamab was associated with cytopenias as described above. Cytopenias were managed through dose delay and/or the administration of G-CSF for neutropenia. Exposure to epcoritamab did not meaningfully impact serum chemistry and clinical laboratory results. In addition, there is no evidence suggestive of drug-induced liver injury.

The FDA's Assessment:

The FDA analysis of worsening hematological and biochemical laboratory values is shown in Table 61. Although shifts in any grade serum chemistry laboratory values did occur while patients were on treatment, these did not rise to a severe level (i.e., worsening to a grade 3 or grade 4). The FDA agrees with the Applicant that the most clinically significant impact of epcoritamab on laboratory results was hematological. Cytopenias were common during treatment with epcoritamab. The evaluation of laboratory data indicates that the frequency of all grade cytopenia and Grade 3-4 cytopenias were higher than those reported as treatment-emergent adverse events. Based on the laboratory data in the primary safety population, Grade 3-4 neutropenia, anemia, and thrombocytopenia occurred in 32%, 12%, and 12% of patients, respectively. The incidence and severity of cytopenias warrant inclusion of a Warning and Precautions for cytopenias in the USPI.

Table 61: FDA Summary of Treatment-emergent Hematology and Chemistry Laboratory Abnormalities in ≥10% of Patients

Laboratory Abnormality	Primary Safety Population		
	Sample Size[a]	All Grades n (%)	Grade 3 or 4[b] n (%)
Hematology			
Decreased Lymphocytes	146	124 (85)	113 (77)
Decreased Hemoglobin	153	95 (52)	19 (12)
Decreased Leukocytes	153	81 (53)	34 (22)
Decreased Neutrophils	148	74 (50)	47 (32)
Decreased Platelets	153	74 (48)	19 (12)
Chemistry			
Decreased Phosphate	152	85 (56)	0
Decreased Sodium	152	85 (56)	4 (3)
Increased AST	151	72 (48)	7 (5)
Increased ALT	152	69 (45)	8 (5)
Decreased Potassium	152	51 (34)	8 (5)
Decreased Magnesium	148	46 (31)	0
Increased Creatinine	152	37 (24)	5 (3)
Increased Potassium	152	32 (21)	2 (1)
Increased Phosphate	152	24 (16)	0
Increased Uric Acid	150	24 (16)	0
Decreased Glucose	151	22 (15)	0
Increased Bilirubin	152	21 (14)	5 (3)
Decreased Calcium	58	6 (10%)	0

Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotransferase
[a] Number of patients with a baseline and at least one post-baseline assessment for lab parameter
[b] Includes shifts from NCI CTCAE Grade <3 to ≥3 and shifts from Grade 3 to Grade 4
Source: FDA Analysis

Drug-induced Liver Injury

The FDA concurs with the Applicant in that 5 (3%) of the patients in the primary safety population experienced AST or ALT >3x upper limit of normal (ULN) and total bilirubin >2xULN within 30 days of the first dose of epcoritamab. The FDA independently confirmed that 4 of these cases did not meet the formal definition of Hy's law given concurrent elevation of serum alkaline phosphatase >2x ULN, leaving one case that met criteria based on labs alone.

- Patient (b) (6): 49 year-old male with Stage III de novo DLBCL who was exposed to 5 doses of epcoritamab with last dose on Day 30. He discontinued

treatment with epcoritamab due to disease progression, suspected on Day 37 but formally diagnosed on Day 44. Death from disease progression occurred on Day 47. Liver function elevations first detected on Day 44, which occurred 14 days after the last dose of epcoritamab and in setting of disease progression.

- He had a history of Grade 1 dyspepsia but no prior history of liver disease. His baseline liver function labs were as follows: AST 27, ALT 13, total bilirubin 6.84 µM/L, and alkaline phosphatase 86.
- Baseline disease at onset of study: Lymphoma involvement at screening included target lesions in the mesenteric and supraclavicular lymph nodes, and adrenal gland.
- Symptoms: Grade 1 abdominal discomfort Day 6 (ongoing), Grade 2 with worsening to Grade 3 abdominal pain Day 23 (ongoing but worsened in context of enterococcal infection), hypoalbuminemia Grade 2 Day 29 (ongoing), Grade 2 nausea Day 44
  - Applicant listed as all unrelated to epcoritamab treatment
- Confounders: CRS Grade 2 Day 27 (ongoing), clinical TLS Grade 1 to Grade 3 Day 33 (ongoing), progressive disease (suspected based on CT on Day 37 but formal diagnosis on Day 44), Grade 3 Enterococcal infection Day 31, CMV infection Day 38
- Pertinent Liver-related lab findings: Table 62

Table 62: FDA Summary of Liver-related Laboratory Abnormalities for Patient (b) (6)

	Day 30[a]	**Day 33**	**Day 37**	**Day 46**
AST (U/L)	36	75	64	145*
ALT (U/L)	31	25	12	65*
Total Bilirubin (µmol/L)	6.84	10.26	10.26	61.56*
Alkaline Phosphatase (U/L)	99	123	162	295

Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotransferase
[a]: Last dose of epcoritamab: 48 mg on Cycle 2 Day 1
*: >3x ULN for AST or ALT, >2x ULN for Total bilirubin or Alkaline Phosphatase

- Assessment: The laboratory abnormalities did not fully meet criteria for Hy's law until Day 46 and appeared to acutely increase to these levels. The last dose of epcoritamab was administered on Day 30, which was 5th dose (Cycle 2 Day 1). Around this time, the patient developed an inflammatory response with Grade 2 CRS on Day 27, Grade 3 enterococcus infection on Day 31, and eventually confirmation of disease progression (Day 37-Day 44). There was no mention of disease involvement in the liver at screening, so a potential tumor flare response is less likely. The disease progression is likely the cause of the findings, with liver function tests abruptly increasing 16 days after the last dose of epcoritamab. However, any contribution from epcoritamab cannot be completely excluded event though it is difficult to extract from the multiple confounders present.

The FDA notes that the chronology of events and clinical and laboratory findings do not definitively support drug-induced liver injury, as other factors may have contributed to the elevated AST and ALT levels. Furthermore, no dose delay, interruptions, or discontinuations were due to hepatotoxicity. At this time, there does not appear to be a notable signal for hepatotoxicity.

Vital Signs

Data:
Vital signs assessed included temperature, pulse rate, oxygen saturation, and blood pressure (systolic and diastolic). Pooled analyses were not performed for vital signs. In the pivotal aNHL expansion cohort of the GCT3013-01 trial, elevated body temperature (>38°C) was reported in 80 (51.0%) subjects, elevated systolic blood pressure was reported for 3 (1.9%) subjects, low (sub normal) systolic blood pressure was reported for 32 (20.4%) subjects, and sub normal oxygen saturation (<92%) was reported for 19 (12.1%) subjects. In the DLBCL expansion cohort of the GCT3013-04 trial, the most common clinically notable vital sign findings were elevated body temperature (75.0%, 27 subjects) and systolic blood pressure below normal (47.2%, 17 subjects)
Information on the presence of fever in the setting of CRS is provided in Section 8.2.5.

The Applicant's Position:
Epcoritamab did not appear to have clinically meaningful adverse effects on vital signs.

The FDA's Assessment:
The FDA notes that changes in vital signs that occur are clinically relevant in the context of patients experiencing CRS following epcoritamab administration. Pyrexia, hypotension, and hypoxia were noted symptoms of CRS (based on adverse event reporting) in 95%, 23%, and 15%

of patients in the primary safety population, respectively.

Electrocardiograms (ECGs)

Data:
In the pivotal aNHL expansion cohort of the GCT3013-01 trial, eight (5.2%) subjects with LBCL had postbaseline abnormal, clinically meaningful ECG abnormalities; most of these abnormalities did not have any specific associated AEs reported.
In the DLBCL expansion cohort of the GCT3013-04 trial, at baseline, 12 (33.5%) subjects had an abnormal ECG result. During the on treatment period overall, 18 (50.0%) subjects had abnormal ECG results; none of these had specific findings reported

The Applicant's Position:
No notable ECG abnormalities potentially associated with epcoritamab were observed.

The FDA's Assessment:
The FDA notes that based on FDA grouping of related preferred terms, cardiac arrhythmias of any grade (based on adverse event reporting) occurred in 10% of patients in the primary safety population, including Grade 3 or 4 cardiac arrhythmias in 0.6%, and therefore met the ≥10% threshold for inclusion in the adverse reaction table in Section 6 of the epcoritamab USPI.

QT

Data:
In the pivotal aNHL expansion cohort of the GCT3013-01 trial, postbaseline QTcF intervals >480 to 500 msec and >500 msec were reported in 4 (4.3%) and 3 (3.2%) subjects with DLBCL, respectively. Of the 3 subjects with QTcF >500 msec, only 1 subject was reported with a TEAE of long QT syndrome, which was not considered related to epcoritamab by the investigator.
In the DLBCL expansion cohort of the GCT3013-04 trial, during the on-treatment period overall, worst QTcF intervals were recorded as >450 to 480 ms for 2 (5.6%) subjects and >480 to 500 ms for 2 (5.6%) subjects. One of the subjects with on-treatment QTcF intervals of >450 to 480 ms and both of the subjects with on-treatment QTcF intervals of >480 to 500 ms had baseline intervals of >450 to 480 ms.

The Applicant's Position:
Epcoritamab does not cause QT prolongation based on the lack of relationship between epcoritamab PK and ΔQTcF, the lack of a biologic mechanism for epcoritamab to directly impact QTcF, and the clinical safety findings that epcoritamab did not have a clinically relevant effect on cardiac repolarization or result in clinically meaningful cardiac TEAEs.

The FDA's Assessment:
The FDA agrees with Applicant's position.

Immunogenicity

Data:
Of the 158 subjects included in the 48 mg Immunogenicity Analysis Set in the Safety Pool 01 LBCL group (subjects assigned to treatment with 48 mg epcoritamab who received at least 1 dose of epcoritamab, including the priming dose; and who had an evaluable baseline ADA sample and 1 or more evaluable on-treatment ADA samples), 4 (2.5%) subjects were ADA positive at baseline. On treatment ADA status was positive for 4 (2.5%) subjects, of which only 1 subject (0.7%) had titer ≥1 (1:320 taking account of all dilutions). Due to the low risk for immunogenicity and the low incidence of samples positive for antibodies to epcoritamab, neutralizing antibodies were not evaluated at this time.
Of the 4 LBCL subjects who were ADA positive on treatment and not at baseline, 2 of the subjects discontinued treatment within the first 2 cycles due to progressive disease, and the other 2 subjects remained on treatment for an additional >10 cycles. No notable safety issues were observed in the 4 ADA-positive subjects.

The Applicant's Position:
The limited data showed no evidence that the presence of ADA impacted safety or tolerability in these subjects.

The FDA's Assessment:
Refer to FDA position in Section 6.3.1.

8.2.5. Analysis of Submission-Specific Safety Issues

8.2.5.1 Cytokine Release Syndrome

Data:
An overview of CRS events at the subject level by safety analysis group is provided in Table 63. A summary of CRS events by epcoritamab dose (ie, priming, intermediate, full dose) is provided in Table 64.
CRS was the most frequent TEAE, experienced by 84 (50.3%) subjects. Almost all subjects (80 out of 84 subjects) experienced a maximum grade 1 or 2 event and there were no grade 4 or 5 cases reported in LBCL subjects. The majority of subjects (68 out of 84 subjects) had an event during the first cycle of treatment after the initial full 48 mg dose on C1D15, with median onset of 19.9 hours following administration of the C1D15 dose. Median time to resolution was 2.0 days (range: 1, 27).

Table 63: Applicant – Summary of AESI: Cytokine Release Syndrome (48 mg Safety Analysis Set – Escalation + Expansion)

Number of Subjects, n (%)	Safety Pool 01[a]		Safety Pool 01+04[a]		
	Primary LBCL (N=167)	DLBCL (N=148)	LBCL (N=208)	DLBCL (N=188)	Supportive All B-NHL (N=374)
Subjects with ≥1 CRS event	**84 (50.3%)**	**73 (49.3%)**	**119 (57.2%)**	**107 (56.9%)**	**230 (61.5%)**
Grade 1	52 (31.1%)	45 (30.4%)	72 (34.6%)	65 (34.6%)	135 (36.1%)
Grade 2	28 (16.8%)	24 (16.2%)	39 (18.8%)	34 (18.1%)	79 (21.1%)
Grade 3	4 (2.4%)	4 (2.7%)	8 (3.8%)	8 (4.3%)	15 (4.0%)
Grade 4	0	0	0	0	1 (0.3%)
Occurrence of any CRS signs and symptoms	**84**	**73**	**119**	**107**	**230**
Fever	83	72	118	106	229
Hypotension	26	24	38	36	76
Hypoxia	16	14	24	21	43
Other[b]	19	18	24	23	63
Subjects with CRS					
Treated with anti-cytokine therapy	25	21	37	33	81
Tocilizumab	25	21	37	33	80
Other anti-cytokine	0	0	0	0	1
Treated with corticosteroid for CRS	18	14	33	29	60
Leading to dose delay/interruption	12	8	15	11	29
Leading to treatment discontinuatic	1	1	1	1	2
Time to first CRS onset (days)					
n	84	73	119	107	230
Mean (SD)	14.5 (7.37)	13.8 (6.06)	13.9 (7.13)	13.4 (6.10)	13.8 (8.22)
Median	16.0	16.0	16.0	16.0	16.0
Min, Max	1, 55	1, 31	1, 55	1, 31	1, 59

Abbreviations: B-NHL = B-cell non-Hodgkin lymphoma; CRS = cytokine release syndrome; DLBCL= diffuse large B-cell lymphoma; iNHL = indolent non-Hodgkin lymphoma; LBCL= large B-cell lymphoma; max = maximum;; MCL = mantle cell lymphoma; ;min = minimum; SD = standard deviation.

Note: CRS events were graded according to (Lee et al., 2019).

[a] Safety Pool 01 includes GCT3013-01. Safety Pool 01+04 includes GCT3013-01 and GCT3013-04. All B-NHL is comprised of the LBCL population plus subjects with iNHL (n=128) and MCL (n=38) from the Dose Escalation and Expansion Parts of the trials.

[b] Other includes the following preferred terms: confusional state, vomiting, dyspnea, chills, dizziness, tachycardia, arthralgia, C-reactive protein increase, sinus tachycardia, rash erythematous, tremor, diarrhea, headache, and nausea (GCT3013-01-EXP-aNHL CSR/Listing 16.2.7.6).

[c] Percentage calculated based on subjects with at least 1 CRS event.

[d] Based on longest recorded CRS duration in subjects with >1 CRS event.

Data cutoff date: 31-Jan-2022

Source: Module 2.7.4 Summary of Clinical Safety Table 5.1

Table 64: Applicant – Summary of Cytokine Release Syndrome Events by Dosing Period (48 mg Safety Analysis Set – Escalation + Expansion)

Safety Pool 01 LBCL (N=167) Number of Subjects, n (%)	Epcoritamab Dosing Period				
	Priming (N=167)	Intermediate (N=163)	First Full (N=156)	Second Full (N=151)	Third Full and after (N=143)
Subjects with at least one CRS event	**11 (6.6%)**	**21 (12.9%)**	**68 (43.6%)**	**7 (4.6%)**	**4 (2.8%)**
Grade 1	8 (4.8%)	17 (10.4%)	42 (26.9%)	5 (3.3%)	2 (1.4%)
Grade 2	3 (1.8%)	4 (2.5%)	22 (14.1%)	2 (1.3%)	2 (1.4%)
Grade 3	0	0	4 (2.6%)	0	0
Occurrence of any CRS signs and symptoms	**11**	**21**	**68**	**7**	**4**
Fever	10	20	68	7	4
Hypotension	2	4	19	2	2
Hypoxia	2	4	11	2	1
Other[b]	2	7	13	1	0
Subject with CRS					
Treated with anti-cytokine therapy	1	5	19	1	2
Tocilizumab	1	5	19	1	2
Other anti-cytokine	0	0	0	0	0
Treated with corticosteroid for CRS	1	3	14	1	1
Leading to dose delay/interruption	0	1	8	2	3
Leading to treatment discontinuation	0	0	0	0	1
Time from most recent dosing(hours)					
n	11	21	68	7	4
Mean (SD)[c]	26.6 (26.75)	66.6 (47.54)	30.7 (28.22)	57.9 (31.84)	74.8 (46.27)
Median	17.2	70.7	19.9	81.0	73.9
Min, Max	12, 105	12, 213	12, 126	19, 86	33, 118

Abbreviations: B-NHL = B-cell non-Hodgkin lymphoma; CRS = cytokine release syndrome; DLBCL= diffuse large B-cell lymphoma; iNHL = indolent non-Hodgkin lymphoma; LBCL= large B-cell lymphoma; max=maximum; MCL = mantle cell lymphoma; min=minimum; SD = standard deviation.

Note: CRS events were graded according to (Lee et al., 2019). Percentages were based on number of treated subjects in the analysis period. For partial CRS onset time, time to CRS onset was imputed as 12 hours if CRS onset date fell on the same date as the most recent dosing date, or CRS onset time was imputed as T00:00 if later than the most recent dosing date. For CRS resolution time, CRS onset and resolution time were imputed as T00:00 and T23:59, respectively, if time component was missing.

[a] Safety Pool 01 includes GCT3013-01. Safety Pool 01+04 includes GCT3013-01 and GCT3013-04. All B-NHL is comprised of the LBCL population plus subjects with iNHL (n=128) and MCL (n=38) from the Dose Escalation and Expansion Parts of the trials.

[b] Other includes the following preferred terms: confusional state, vomiting, dyspnea, chills, dizziness, tachycardia, arthralgia, C-reactive protein increase, sinus tachycardia, rash erythematous, tremor, diarrhea, headache, and nausea (GCT3013-01-EXP-aNHL CSR/Listing 16.2.7.6).

[c] Based on the first CRS in subjects with >1 CRS event within the dosing period.

[d] Percentage calculated based on subjects with at least 1 CRS event.

[e] Based on longest recorded CRS duration in subjects with >1 CRS event.

Data cutoff date: 31-Jan-2022

Source: Module 2.7.4 Summary of Clinical Safety Table 5.2

Evaluation of Tocilizumab Use in CRS Management:

Of the 123 CRS events of any grade that were reported, 31 (25.2%) were managed by tocilizumab treatment. Among the 31 CRS events where tocilizumab was administered, 5 (16.1%) were grade 1, 22 (71.0%) were grade 2, and 4 (12.9%) were grade 3. Among all treatment-emergent CRS events, most (94.0%) grade 1 events were not treated with tocilizumab, while most grade 2 (62.9%) and all (100%) grade 3 CRS events were treated with tocilizumab, consistent with the protocol recommendation to use tocilizumab to treat grade 3 or 4 CRS as well as grade 1 or 2 CRS in older subjects or subjects with extensive comorbidities. Among the 31 CRS events in which tocilizumab was administered, most (27; 87.1%) events responded to tocilizumab. The tocilizumab response rate was 80.0%, 90.9%, and 75.0% for CRS of grade 1, 2, and 3, respectively.

Other Concomitant Medication Use in CRS Management

In addition to corticosteroids and tocilizumab, other concomitant medications, such as antipyretics, antibiotics, oxygen, and intravenous fluids, were used to manage CRS. In the Safety Pool 01 LBCL group, tocilizumab was administered in 15.0% of subjects and corticosteroids (beyond those scheduled for CRS prophylaxis) in 10.8% of subjects at any time during the treatment period. The most common other therapies (administered to ≥5% of subjects) for CRS were paracetamol (32.3%), sodium chloride (saline) (9.6%), oxygen (6.6%), and piperacillin sodium:tazobactam sodium (6.6%). These medications were mostly given during the Week ≤8 period.

Additional Evaluation of Potential CRS Events

A total of 8 potential CRS events (based on FDA criteria) occurred in 7 subjects, all from the GCT3013-01 pivotal aNHL expansion cohort. The sponsor's adjudication was aligned with the investigators: all 8 potential events were adjudicated as not CRS due to alternate etiology for the symptoms including fever, hypotension, and/or hypoxia.

The Applicant's Position:

An important identified risk associated with epcoritamab therapy is CRS (which were mostly grade 1 or 2), which is considered manageable with appropriate preventative measures via the product labeling and additional educational materials. These include warning and precautions for healthcare providers and risk minimization measures including corticosteroid administration prior to and after epcoritamab dosing during the first cycle of treatment, monitoring during treatment, comprehensive supportive care, and dose delays for AEs.

The FDA's Assessment:

The Applicant reported and graded CRS events according to the ASTCT consensus criteria (Lee et al, 2019). Risk mitigation measures employed in the pivotal trial GCT3013-01 and supportive trial GCT3013-04 included guidelines on management, premedication, prophylactic corticosteroids, hospitalization, and monitoring.

Prophylaxis:
All patients received premedication for cycle 1, which consisted of administration of corticosteroids (prednisolone 100 mg IV or PO or dexamethasone 15mg IV), antihistamines, and antipyretics 30 to 120 minutes prior to each of the first 4 administrations of epcoritamab. Due to the observation of continued Grade 2 CRS with day 1 premedication alone, corticosteroids are continued for 3 consecutive days following administration of epcoritamab in cycle 1 in addition to the administration prior to the study drug. For later doses of epcoritamab (Cycle 2 onward), premedication and CRS prophylaxis were optional based on the prior occurrence of Grade ≥2 CRS and investigator discretion.

Hospitalization Requirements
Administration of epcoritamab occurred in a clinical setting with immediate access to intensive care, in addition to neurology and nephrology consultation services in both the pivotal study GCT3013-01 and the supportive study GCT3013-04. For all patients, hospitalization was only required for a minimum of 24 hours (minimum of 72 hours for supportive population who are part of dose escalation in GCT3013-01) after administration of the first full 48 mg dose of epcoritamab on Cycle 1 Day 15. Otherwise, patients were to remain in the treatment facility following injection for a minimum of 2 hours for monitoring. Therefore, except for the first full dose of epcoritamab, the data from both the primary safety population and supportive safety population represent subcutaneous administration of epcoritamab in an outpatient healthcare setting with post-injection monitoring and access to intensive care.

The FDA safety analysis for CRS in the context of epcoritamab assessed the events reported by the Applicant in the ADCRS dataset, which also contained potential cases of CRS that were not initially identified by the investigator. The sections below discuss this analysis.

CRS Incidence and Severity
An overview of the CRS incidence and severity in both the primary and supportive safety populations is provided in Table 65. In the primary safety population, 51% of patients (80/157) experienced a CRS event, with 29% (46/218) considered serious. As outlined in Table 66, the most frequently reported CRS signs and symptoms of the 116 events in the 80 patients with CRS from the primary Safety population included pyrexia (95%), hypotension (23%), and respiratory symptoms without hypoxia (16%) or with hypoxia (15%). Neurologic adverse events occurring concurrently with CRS were observed in 4% (5/157) of patients and included ataxia, confusion, dizziness, and tremor. Most patients with CRS experienced either Grade 1 or Grade 2 CRS at 37% (58/157) and 17% (27/157), respectively. Three percent of patients (4/157) experienced grade 3 CRS with no patients in the primary safety population experiencing a Grade 4 or Grade 5 event. Although 15% (24/157) of patients experienced more than one CRS event, the recurrent episode was of a higher grade in only 3% (5/157) and all cases were an increase from Grade 1 to Grade 2 in severity. Despite over half of patients experiencing CRS, few CRS events impacted treatment with epcoritamab; 7% (11/157) patients required a dose

delay and 0.6% (1/157) required cessation of study treatment. Ninety-eight percent of the 116 CRS events resolved.

The incidence of CRS in the supportive safety population was slightly higher (63%) than in the primary safety population, with 35% of events being serious CRS events. This increase in occurrence, which also worsened in severity, is likely due to inclusion of R/R MCL patients, who have an increased risk of CRS relative to patients with R/R LBCL. Otherwise, the other findings outlined in Table 65 characterizing CRS are similar between both populations.

Table 65: FDA Overview of CRS in Patients in the Primary and Supportive Safety Populations

		Primary Safety Population N=157 n, (%)	Supportive Safety Population N=374 n, (%)
Patients with any Grade CRS		80 (51)	234 (63)
CRS by Grade	Grade 1	58 (37)	169
	Grade 2	27 (17)	86
	Grade 3	4 (3)	15
	Grade 4	0	1
	Grade 5	0	0
Patients with any Serious CRS		46 (29)	131 (35)
Patients >1 CRS event[b]		24 (15)	85 (22)
Recurrence to higher grade[c]		5 (3)	25 (7)
Resolution of CRS event (n=116 events and n=244)		114 (98)	242 (99)
Effect on Treatment	Delay	11 (7)	29 (8)
	Discontinuation	1 (0.6)	2 (0.5)

Abbreviations: AE, adverse event; CRS, cytokine release syndrome
[a] CRS data derived from ADCRS dataset
[b] Recurrence counted if following separate epcoritamab dose
[c] All recurrent events of higher grade were Grade 1 CRS recurring as Grade 2 CRS in primary population. In supportive population, recurrent CRS of higher grade were the following: 20 cases Grade 1 to Grade 2, 2 cases Grade 1 to Grade 3, 2 cases Grade 2 to Grade 3, and 1 case Grade 2 to Grade 4.
Source: FDA Analysis

Table 66: FDA Summary of Symptoms in Patients with CRS of Any Grade in the Primary Safety Population

Symptom		CRS Events N=116 n (%)
Hospitalization for CRS[a]		62 (53)
Fever		110 (95)
Hypotension		27 (23)
Respiratory[b]		19 (16)
Hypoxia		17 (15)
Other Symptom Flag	Constitutional	9 (8)
	Cardiovascular[c]	7 (6)
	Neurological[d]	5 (4)
	Gastrointestinal	2 (2)
	Skin	1 (0.9)

Abbreviations: CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome
[a] Not counted if already hospitalized for mandatory 24 hours following first full 48 mg dose or for another cause
[b] Respiratory symptom such as dyspnea without associated hypoxia
[c] Tachycardia
[d] Tremor, confusion, ataxia, dizziness not attributed to concurrent ICANS
Source: FDA Analysis

Timing of CRS

The FDA analysis of the timing of CRS by dose is presented in Table 67. Of the 116 CRS events, most (92%) occurred within Cycle 1. CRS was most common after the first full 48 mg dose of epcoritamab, where 45% (66/148) of patients experienced CRS of any grade. For the other doses in Cycle 1, CRS occurred in 6% (9/157) after the 0.16 mg dose on Cycle 1 Day 1, 16% (19/154) after the 0.8 mg dose on Cycle 1 Day 8, and 5% (7/145) after the 48 mg dose on Cycle 1 Day 22. Outside of Cycle 1, CRS events were reported in 1 to 2 patients, equating to 0.8-1% of patients, and were mostly Grade 1 in severity.

The median time to onset of CRS from the most recent administered dose of epcoritamab

across all doses was 20.5 hours, ranging from 0 to 10 days, while the median time of onset post the Cycle 1 Day 15 dose was 20 hours, ranging from 0-7 days. The median duration of CRS was 2 days (range: 1 to 27 days), with 75% of events lasting 3.4 days or less. Of note, differences in timing calculations between the Applicant and FDA analyses were due to the latter counting CRS resolving on the same day as 0 instead of 1 day or 0 instead of an assumption of 12 hours.

Table 67: FDA Overview of CRS by Dose in the Primary Safety Population (N=157)[a]

CRS Grade	All Tx[a]	Cycle 1[a] Step-up and target doses				Cycle 2[a] 48 mg				Cycle 3[a] 48 mg				Cycle 4[a] 48 mg
		D1 0.16 mg	D8 0.8 mg	D15 48 mg	D22 48 mg	D1	D8	D15	D22	D1	D8	D15	D22	D1
Any	80 (51)	9 (6)	19 (12)	66 (45)	7 (5)	2 (1)	1 (0.8)	1 (0.8)	1 (0.9)	1 (0.9)	1 (0.9)	0	1 (1)	1 (1)
1	58 (37)	7 (4)	15 (10)	43 (28)	5 (3)	2 (1)	0	1 (0.8)	1 (0.9)	(0.9)	0	0	0	1 (1)
2	27 (17)	2 (1)	4 (3)	20 (14)	2 (1)	0	1 (0.8)	0	0	0	1 (0.9)	0	1 (1)	0
3	4 (3)	0	0	4 (3)	0	0	0	0	0	0	0	0	0	0

Results reported: N (%), denominator: patient exposed to epcoritamab (all treatment) or at a particular dose (Cycle 1 Day 1).
Note: a patient may have had multiple CRS episodes
Abbreviations: Tx, treatment; D, day
[a] Denominators varied: All treatment 157, Cycle 1 (C1)D1 157, C1D8 154, C1D15 148, C1D22 145, C2D1 136, C2D8 128, C2D15 118, C2D22 114, C3D1 109, C3D8 108, C3D22 103, C4D1 94
Source: FDA Analysis

Management of CRS

Per the protocol, management of CRS was based on the ASTCT guidelines and included interruption of epcoritamab (as applicable), supportive therapy, anti-cytokine therapy (tocilizumab, siltuximab), corticosteroid therapy, and extending premedication beyond Cycle 1. Anti-cytokine therapy and corticosteroids could be considered in select cases of Grade 1 CRS, such as those in patients with advanced age, high tumor burden, circulating tumor cells, or with fever refractory antipyretics. For patients with Grade 2 CRS, anti-cytokine therapy was recommended followed by corticosteroids or increased dose of anti-cytokine treatment if the CRS was refractory. Administration of tocilizumab and corticosteroids were prespecified for Grade 3 and Grade 4 CRS.

The management of CRS in patients in the primary safety population is outlined in Table 68. Tocilizumab in combination with other agents, such as oxygen or steroids, was the most common intervention outside of hospitalization. As expected, all cases of Grade 3 CRS were

treated with tocilizumab, although only one was also treated with concurrent corticosteroids.

Since the use of tocilizumab and/or corticosteroids were not prespecified for Grade 1 or Grade 2 CRS, there was heterogeneity in the patient cases that received tocilizumab versus those who did not receive tocilizumab as shown in Table 68 to Table 71, precluding any meaningful interpretation of the data. Further, 98% (114/116 events) of CRS resolved and the outcomes in patients treated with tocilizumab and those not treated with tocilizumab were similar. Therefore, the use of tocilizumab and corticosteroids for the management of epcoritamab-induced CRS, especially Grade 1 and 2 CRS, remains uncertain and further prospective evaluation is warranted

Table 68: FDA Summary of Management for CRS in Patients in the Primary Safety Population

Intervention	Any Grade CRS[a] N=116 events	Grade 1 CRS N=78 events	Grade 2 CRS N=32 events	Grade 3 CRS N=4 events
Hospitalization[b]	62 (53%)	39 (50%)	19 (59%)	100%
Steroids only	9 (7.8%)	6 (7.7%)	3 (9.4%)	0
Oxygen only	3 (2.6%)	0	3 (9.4%)	0
Steroids + oxygen	1* (0.9%)	0	0	0
Tocilizumab only	10 (8.6%)	3 (3.9%)	7 (22%)	0
Tocilizumab only or in combination	27 (23%)	4 (5.1%)	19 (59%)	4 (100%)
Tocilizumab + oxygen	5 (4.3%)	0	5 (16%)	0
Tocilizumab + steroids	6 (5.2%)	1 (1.3%)	5 (16%)	0
Tocilizumab + vasopressors	2 (1.7%)	0	0	2 (50%)
Tocilizumab + oxygen + steroids	1 (0.9%)	0	1 (3.1%)	
Tocilizumab + oxygen + vasopressors	1 (0.9%)	0	0	1 (25%)
Tocilizumab + steroids + oxygen + vasopressors	1 (0.9%)	0	0	1 (25%)

Tocilizumab + steroids + oxygen + vasopressors + dialysis	1 (0.9%)	0	1 (3.1%)	0

[a] 2 CRS events did not have grade specified
[b] Not counted if already hospitalized for mandatory 24 hours following first full 48 mg dose or for another cause
Source: FDA Analysis

Table 69: FDA Summary of Symptoms of Patients with CRS Treated or Not Treated with Tocilizumab in the Primary Safety Population

Symptom		Overall CRS[a] N=116 events	Grade 1 CRS		Grade 2 CRS		Grade 3 CRS[b] N=4
			No Toci N=74	Toci N=4	No Toci N=13	Toci N=19	
Hospitalization for CRS[c]		62 (53%)	35 (47%)	3 (75%)	6 (46%)	14 (74%)	3 (75%)
Fever		110 (95%)	74 (100%)	4 (100%)	9 (69%)	19 (100%)	4 (100%)
Hypoxia		17 (15%)	0	0	5 (38%)	10 (53%)	2 (50%)
Respiratory[d]		19 (16%)	1 (1.4%)	1 (25%)	5 (38%)	10 (53%)	2 (50%)
Hypotension		27 (23%)	3 (4.1%)	0	8 (62%)	13 (68%)	4 (100%)
Other Symptom Flag	Cardiovascular[e]	7 (6.0%)	2 (2.7%)	1 (25%)	0	4 (21%)	0
	Neurological[f]	5 (4.3%)	3 (4.1%)	0	0	2 (11%)	0
	Gastrointestinal	2 (1.7%)	1 (1.4%)	0	0	1 (5.3%)	0
	Skin	1 (0.9%)	1 (1.4%)	0	0	0	0
	Constitutional	9 (7.8%)	4 (5.4%)	1 (25%)	0	4 (21%)	0

Symptom	Overall CRS[a] N=116 events	Grade 1 CRS		Grade 2 CRS		Grade 3 CRS[b] N=4
		No Toci N=74	Toci N=4	No Toci N=13	Toci N=19	

Abbreviations: CRS, cytokine release syndrome; Toci, tocilizumab; ICANS, immune effector cell-associated neurotoxicity syndrome
[a] 2 CRS events did not have a grade specified
[b] All Grade 3 CRS was treated with tocilizumab
[c] Not counted if already hospitalized for mandatory 24 hours following first full 48 mg dose or for another cause
[d] Respiratory symptom such as dyspnea without associated hypoxia
[e] Tachycardia
[f] Tremor, confusion, ataxia, dizziness not attributed to concurrent ICANS
Source: FDA Analysis

Table 70: FDA Summary of CRS Grade and Duration Based on Treatment with Tocilizumab in the Primary Safety Population

		All CRS	Tocilizumab	No Tocilizumab
Total CRS events of any grade		116	27	80
Grade 1 (n, % events)		78 (67)	4 (5)	74 (95)
Grade 2 (n, % event)		32 (28)	19 (59)	13 (41)
Grade 3 (n, % events)		4 (3)	4 (100)	0
Duration of CRS (days)	Median	2	2	2
	Range	1-27	1-12	1-27
	Q3	3.4	4	3

Abbreviations: CRS, cytokine release syndrome; Q3: 75% quartile
Source: FDA Analysis

Table 71: FDA Summary of the Onset, Duration, and Resolution of Grade 2 CRS Occurring in the Primary Safety Population Based on Tocilizumab Treatment

Tocilizumab use in Grade 2 CRS	CRS onset from last dose	CRS Duration	Resolution (% of events)
No Tocilizumab (n=13)	12h (1-120h)	2.5d (1-27)	92%
Tocilizumab (n=19)	21h (1-168h)	2d (1-12)	100%

Abbreviations: CRS, cytokine release syndrome; h, hours; d, days
Source: FDA Analysis

Risk Mitigation

Based on the CRS profile with epcoritamab, a Boxed Warning for CRS is warranted along with a corresponding medication guide. This recommendation is based on the occurrence of serious and life-threatening cases of CRS observed and the need for providers to be accurately aware of the risk. The USPI includes the statement that epcoritamab should only be administered by a qualified healthcare professional with appropriate medical support to manage severe reactions such as cytokine release syndrome, which is appropriate. The management of CRS in relation to epcoritamab will also be included in the USPI. In addition to these items, the FDA will include in the USPI to require hospitalization after the first full 48 mg dose of epcoritamab, which occurs on Cycle 1 Day 15, as this was the guidance in place for all patients in the primary safety population who represent the indicated population and is the dose most frequently associated with CRS.

(b) (4)

USPI should recommend management per current practice guidelines and to provide supportive therapy, including intensive care as applicable. There is a need for prospective evaluation to determine the optimal use of corticosteroids and tocilizumab in the management of epcoritamab-induced CRS.

8.2.5.2 Immune Effector-cell Associated Neurotoxicity Syndrome

Data:

Scheduled neurologic assessments for ICANS were conducted in all epcoritamab clinical trials. In the Expansion Part of the GCT3013-01 trial and in the GCT3013-04 trial, ICANS events were graded according to ASTCT criteria (Lee et al, 2019). In order to proactively monitor the potential occurrence of ICANS, ICE assessments were required to be performed during therapy by the trial site staff at baseline, during every visit, and at end of treatment. During the scheduled hospitalization in Cycle 1, the ICANS assessment had to be performed once daily. ICANS assessment was also required daily in case of unscheduled hospitalization due to symptoms associated with CRS. In the Dose Escalation Part of the GCT3013-01 trial, neurological assessment was conducted according to the CARTOX-10 scale (Neelapu et al., 2017), and the AESI of suspected immune-mediated neurologic symptoms consistent with ICANS was captured under the reported PT (graded by CTCAE). However, none of the subjects in the Dose Escalation Part of the GCT3013-01 trial identified as having AESI of suspected immune-mediated neurologic symptoms consistent with ICANS were among the subjects in the 48 mg Safety Analysis Set included in this safety analysis.

Overall, the ICANS grade was determined by the most severe event of the neurotoxicity domains (ICE score, level of consciousness, seizure, motor findings, raised intracranial pressure/cerebral edema) not attributable to any other cause. A summary of ICANS is provided in Table 72.

Table 72: Applicant – Summary of AESI: Immune Effector Cell-Associated Neurotoxicity Syndrome (48 mg Safety Analysis Set – Escalation + Expansion)

Number of subjects (%)	Safety Pool 01[a]		Safety Pool 01+04[a]		
	Primary LBCL (N=167)	DLBCL (N=148)	LBCL (N=208)	DLBCL (N=188)	Supportive All B-NHL (N=374)
Subjects with ≥1 ICANS event	**10 (6.0%)**	**9 (6.1%)**	**11 (5.3%)**	**10 (5.3%)**	**23 (6.1%)**
Grade 1	7 (4.2%)	6 (4.1%)	8 (3.8%)	7 (3.7%)	16 (4.3%)
Grade 2	2 (1.2%)	2 (1.4%)	2 (1.0%)	2 (1.1%)	6 (1.6%)
Grade 3	0	0	0	0	0
Grade 4	0	0	0	0	0
Grade 5	1 (0.6%)	1 (0.7%)	1 (0.5%)	1 (0.5%)	1 (0.3%)
Worst on-treatment ICE score					
10	3 (1.8%)	2 (1.3%)	3 (1.4%)	2 (1.1%)	4 (1.1%)
7-9	5 (3.0%)	5 (3.4%)	6 (2.9%)	6 (3.2%)	14 (3.8%)
3-6	1 (0.6%)	1 (0.7%)	1 (0.5%)	1 (0.5%)	4 (1.1%)
0-2	0	0	0	0	0

Number of subjects (%)	Safety Pool 01[a]		Safety Pool 01+04[a]		
	Primary LBCL (N=167)	DLBCL (N=148)	LBCL (N=208)	DLBCL (N=188)	Supportive All B-NHL (N=374)
Missing	1 (0.6%)	1 (0.7%)	1 (0.5%)	1 (0.5%)	1 (0.3%)
Subjects with ICANS event					
Leading to dose delay	3 (1.8%)	3 (2.0%)	3 (1.4%)	3 (1.6%)	5 (1.3%)
Leading to treatment discontinuation	1 (0.6%)	1 (0.7%)	1 (0.5%)	1 (0.5%)	1 (0.3%)
Time to first ICANS onset (days)					
n	10	9	11	10	23
Mean (SD)	29.0 (39.60)	30.4 (41.72)	26.8 (38.25)	27.9 (40.15)	25.7 (28.54)
Median	16.5	17.0	16.0	16.5	16.0
Min, Max	8, 141	8, 141	5, 141	5, 141	5, 141
Time to ICANS resolution (days)					
Subjects with resolved ICANS[b]	9 (90.0%)	8 (88.9%)	10 (90.9%)	9 (90.0%)	22 (95.7%)
Mean (SD)[c]	5.0 (3.77)	4.5 (3.70)	4.8 (3.61)	4.3 (3.50)	3.7 (3.06)
Median	5.0	3.5	4.0	3.0	2.0
Min, Max	1, 9	1, 9	1, 9	1, 9	1, 9

Abbreviations: DLBCL= diffuse large B-cell lymphoma; ICE = immune effector cell-associated encephalopathy assessment tool; iNHL = indolent non-Hodgkin lymphoma; LBCL= large B-cell lymphoma; MCL = mantle cell lymphoma; SD = standard deviation.

Note: ICANS were graded according to (Lee et al., 2019).

[a] Safety Pool 01 includes GCT3013-01. Safety Pool 01+04 includes GCT3013-01 and GCT3013-04. All B-NHL is comprised of the LBCL population plus subjects with iNHL (n=128) and MCL (n=38) from the Dose Escalation and Expansion Parts of the trials.

[b] Percentage calculated based on subjects with at least 1 ICANS event.

[c] Based on longest recorded CRS duration in subjects with >1 ICANS event.

Data cutoff date: 31-Jan-2022

Source: Module 2.7.4 Summary of Clinical Safety Table 5.5

The Applicant's Position:

ICANS is considered an important identified risk, consistent with the mechanism of action of epcoritamab. Most cases (9 out of 10 subjects) were grade 1 or 2, and the median time to onset was 16.5 days, which correlates with the timing of the first full 48 mg dose on C1D15. One (0.6%) subject had a fatal (grade 5) ICANS event that was considered related to epcoritamab by the investigator and occurred in a subject with several confounding conditions including disease progression. All other episodes resolved with a median time to resolution of 5.0 days. Seven of the 10 ICANS events overlapped with CRS events. This important identified risk will be managed via the product labeling and additional educational materials. These include warnings and precautions for healthcare providers and risk minimization measures, including corticosteroid administration prior to and after epcoritamab dosing during the first cycle of treatment, monitoring during treatment, comprehensive supportive care, and dose delays for AEs

The FDA's Assessment:

As stated by the Applicant, ICANS was graded according to ASTCT criteria (Lee et al, 2019) and managed per ASTCT guidelines. To identify ICANS, both the pivotal trial GCT3013-01 and supportive trial GCT3013-04 outlined scheduled neurological assessments, which included the 10-point immune effector cell-associated encephalopathy (ICE) score, at baseline, prior to each dose of epcoritamab, and at the end of treatment. Additional assessments were performed during the mandatory hospitalization following the first full 48 mg dose on Cycle 1 Day 15 and during the hospitalization for or upon endorsement of neurological signs or symptoms associated with CRS. Risk mitigation included corticosteroid pretreatment during Cycle 1 of therapy and monitoring post epcoritamab dose. As part of monitoring, hospitalization was only required following the first full 48 mg dose on Cycle 1 Day 15. Otherwise, patients were observed for a minimum of 2 hours after administration of study drug.

The FDA safety analysis for ICANS associated with epcoritamab monotherapy was based on independent analysis of the safety datasets for both the primary and supportive safety population using the preferred term ICANS. Based on the FDA analysis, which is shown in Table 73, ICANS occurred in 10 patients (6%) in the primary safety population. Nine of the 10 patients experienced low grade events with the majority being Grade 1 in severity in 7 patients (5%) followed by Grade 2 in 2 patients (1%). The 1 severe ICANS was fatal. Nine of the 10 ICANS cases (90%) occurred within the first 28 days of therapy with a median onset of 16.5 days (range 8-141 days). Clinical manifestations included, but were not limited to, confusional state, lethargy, tremor, dysgraphia, aphasia, and non-convulsive status epilepticus. Except for the fatal case, all ICANS events resolved with a median duration of 4 days (range 0-8 days). Four patients were treated with corticosteroids and one patient with tocilizumab in addition to other measures of supportive care per ASTCT guidelines.

Similar findings were observed in the larger supportive safety population with the exception of a shorter median duration of ICANs of 1 day. This difference may be related to the much lower number of events in the primary safety population.

The FDA concurs with the Applicant that ICANS is an identified risk associated with the mechanism of action of epcoritamab given that it is a bispecific T-cell engaging antibody. However, the FDA does not agree with the Applicant's position that the risk can be sufficiently managed via the premedication with corticosteroids in Cycle 1, monitoring during treatment, proposed labeling, and educational materials. The serious and sometimes fatal events that have occurred in the context of epcoritamab administration warrant a Boxed Warning for ICANS in the USPI in order to appropriately inform prescribers and the medical team of the risk.

Table 73: FDA Analysis of ICANS in the Primary and Supportive Safety Populations

		Primary Safety Population N=157 n, (%)[a]	Supportive Safety Population N=374 n, (%)[a]
Patients with any Grade ICANS		10 (6)	23 (6)
Grade 1		7 (5)	16 (5)
Grade 2		2 (1)	6 (2)
Grade 3		0	0
Grade 4		0	0
Grade 5		1 (0.6)	1 (0.3)
Resolution of ICANS event (n, % of patients with ICANS)		9 (90)	22 (96)
Effect on Treatment	Delay	3 (1.9)	5 (1.3)
	Discontinuation	1 (0.6)	1 (0.3)
Timing Days (range) Q3	Onset	16.5 (8-141) 22.3	16.5 (5-141) 22
	Duration[b,c]	4 (0-8) 8	1 (0-8) 4

Abbreviations: ICANS, immune effector cell-associated neurotoxicity syndrome; Q3, 75% quartile
[a] Given low incidence, percentages rounded to nearest 1/10th decimal if incidence below 5%.
[b] Duration calculated based following removal of Grade 5 event.
[c] Duration differs from Applicant as same day designated as 0 rather than 1.
Source: FDA Analysis

8.2.5.3 Clinical Tumor Lysis Syndrome

Data:

A diagnosis of TLS required that 2 or more of the following metabolic abnormalities occurred within 3 days before or up to 7 days after the initiation of therapy: hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia. CTLS was present when laboratory TLS was accompanied by an increased creatinine level, seizures, cardiac dysrhythmia, or death. Frequency and severity of CTLS was consistent in the Safety Pool 01 LBCL group and the All B-NHL group.

In the Safety Pool 01 LBCL group, 3 (1.8%) subjects experienced TLS. In 2 (1.2%) subjects, the events met the criteria for CTLS and in both subjects the CTLS was grade 3. Both events of CTLS occurred in the setting of disease progression and were unresolved at time of subject death.

The Applicant's Position:
The safety profile of epcoritamab, including the incidence of CTLS, is consistent with the mechanism of action of epcoritamab, and is considered manageable with appropriate monitoring and mitigation measures.

The FDA's Assessment:
The FDA agrees with Applicant's position. Cases of clinical TLS occurred at a low incidence. The FDA did not agree (b) (4)
(b) (4)

8.2.5.4 Serious Infection Events

Data:
Serious TEAEs of infection were reported in 27 (16.2%) subjects in the Safety Pool 01 LBCL group. Serious TEAEs of infection reported for 2 or more subjects included pneumonia and sepsis in 4 (2.4%) subjects; COVID-19, COVID-19 pneumonia, and cellulitis in 3 (1.8%) subjects each; bacteremia, septic shock, and upper respiratory tract infection in 2 (1.2%) subjects each. Four (2.4%) subjects had fatal infections (COVID-19 [1.2%], and COVID 19 pneumonia [0.6%], and PML [0.6%]), none of which were considered related to epcoritamab by the investigator.

The Applicant's Position:
Serious infections are an important potential risk with epcoritamab, due to its mechanism of action, and are generally manageable with antimicrobial therapy.

The FDA's Assessment:
The FDA safety analysis focusing on infections is presented in Table 74. Sixteen percent of infections were serious with most of these attributed to sepsis. Three infections resulted in death, 2 of which were due to COVID-19 and 1 due to progressive multifocal encephalopathy (PML). Although confounders are present in all 3 cases, such as prior rituximab in the case of PML and the ongoing pandemic in the case of the COVID-19 deaths, the potential contribution of epcoritamab to the severity of the events is unclear, especially given that the population is from a single-arm trial.

The FDA notes that the main differences between the FDA analysis and the Applicant's stem from FDA's use of FDA grouped preferred terms and the smaller primary safety population. Taking these reasons into account, the FDA agrees with Applicant's position that the infections, specifically serious infections, are an important potential risk with epcoritamab therapy and are likely due, at least in part, to the study drug's mechanism of action. While the use of antimicrobial therapy is helpful in the treatment of some infections, the FDA will recommend

that the USPI contain a Warnings and Precaution for Infections, advise prophylaxis for Pneumocystis jirovecii, and consider prophylaxis against herpes virus (see Section 8.1.2 under concomitant medications for additional information on prophylaxis in Study GCT3013-01) .

Table 74: FDA Analysis of Infections in the Primary Safety Population

Primary Safety N=157 n, %				
	Any Grade	Grade 3-4	Serious	Fatal
Infections and Infestations (SOC)	71 (45)	23 (15)	25 (16)	3 (2)
Preferred Term				
Urinary Tract Infection	13 (8)	3 (2)	3 (2)	0
COVID-19	10 (6)	6 (4)	5 (3)	2 (1)
Sepsis	9 (6)	9 (6)	9 (6)	0
Upper Respiratory Tract Infection	9 (6)	2 (1)	3 (2)	0
Pneumonia	8 (5)	2 (1)	3 (2)	0
Herpesvirus Infection	6 (4)	0	2 (1)	0
Oral Candidiasis	5 (3)	0	0	0
Cellulitis	4 (3)	3 (2)	3 (2)	0
Gastroenteritis	3 (2)	0	0	0
Progressive Multifocal Leukoencephalopathy	1 (0.6)	0	1 (0.6)	1 (0.6)

Abbreviations: SOC, system organ class
Source: FDA Analysis

8.2.5.5 Neurological Events

Data:
Treatment-emergent neurological events were analyzed using two approaches, as recommended by FDA: a definition provided in Topp et al, 2015 and a broad definition that included all PTs classified under the SOC of nervous system disorders or psychiatric disorders, excluding high-level group terms of sleep disorders and disturbances, and peripheral neuropathies. ICANS is included as one of the PTs in both searches and is discussed separately in Section 8.2.5.2.
In the Safety Pool 01 LBCL group (N=167) using the Topp et al, 2015 definition, 43 (25.7%) subjects experienced at least 1 neurological event. PTs reported in ≥2% subjects included ICANS (6.0%; 10 subjects), dizziness (5.4%; 9 subjects), paresthesia (3.6%; 6 subjects), and tremor (3.6%; 6 subjects). All neurological events using the Topp et al, 2015 definition were grade 1 or 2 in severity except for the following reported for 1 subject each: ICANS (grade 5), loss of consciousness (grade 5), facial paralysis (grade 3), and delirium (grade 3). Of note, except for ICANS, all grade 3 or higher events were considered unrelated to epcoritamab by the investigator. Most of the neurological events using the Topp et al, 2015 definition occurred in the first 2 cycles of treatment (Week ≤8; 33 of 43 subjects).
Using the broad definition for neurological events 59 (35.3%) subjects had neurological events. PTs reported in ≥2% subjects included headache (12.6%; 21 subjects), ICANS (6.0%; 10 subjects), dizziness (5.4%; 9 subjects), paresthesia (3.6%; 6 subjects), tremor (3.6%; 6 subjects), and anxiety (2.4%; 4 subjects). Most of the neurological events using the broad definition occurred in the first 2 cycles of treatment (Week ≤8; 50 of 59 subjects).
A small portion of neurological events (using both definitions) were concurrent with CRS (8% to 11%) in the Safety Pool 01 LBCL group.

The Applicant's Position:
The majority of neurological events were coded to headache (12.6%; 21 subjects), ICANS (6.0%; 10 subjects) and dizziness (5.4%; 9 subjects). The ICANS events were a maximum of grade 1 (4.5%; 7 subjects), or grade 2 (1.2%; 2 subjects) There were no grade 3 or 4 events. One (0.3%) subject had a fatal ICANS event (grade 5). The median time to onset of ICANS was 16.5 days from initiation of epcoritamab. The ICANS events resolved in 9 of 10 subjects, with a median time to resolution of 5 days. The onset of ICANS can be concurrent with CRS, following resolution of CRS or in the absence of CRS.

The FDA's Assessment:
The FDA safety analysis of neurological adverse events is shown in Table 75. An event was considered a potential neurological adverse event if it was included in either the system organ class of Neurological Disorders or Psychiatric disorders and did not occur in the context of ICANS or CRS. For neurological adverse events occurring in the context of ICANS or CRS, refer to pertinent sections above.

The FDA analysis is similar to the Applicant's analysis based on the broad definition of

neurological adverse events. However, the former has somewhat higher incidence of overall neurological adverse events due to inclusion of PTs such as insomnia. While the FDA analysis resulted in a higher number of any grade neurological adverse events compared to the Applicant's, the FDA concurs with the Applicant's position that the majority of the events were Grade 1 or 2 in severity with few serious (6%) or Grade 3 or 4 events (4%). Isolated fatal neurological adverse events were very rare with only 1 (0.6%) observed in the FDA analysis and likely attributable to progressive disease as discussed below:

- *Patient* (b) (6): The 1 fatal neurological adverse event was a Grade 5 "loss of consciousness," which occurred in a 54 year-old male patient with Stage IV transformed DLBCL who died on day 119 of therapy following 12 doses of epcoritamab. Based on the patient narrative, the loss of consciousness was potentially due to a complication of progressive disease and less likely a direct effect of epcoritamab. The patient developed progressive disease, confirmed by PET/CT on Day 43, and although he received epcoritamab until day 85, the patient continued to have worsening disease with development of malignant Grade 3 pericardial and pleural effusions. Following discontinuation of therapy with epcoritamab on Day 85, the patient was treated with prednisone, antimicrobials, and pain control. A CT scan of the thorax approximately 10 days after discontinuation of study treatment revealed continued progression of disease. Fourteen days after completion of study treatment the patient experienced an acute neurological decline denoted as loss of consciousness. An autopsy was not performed, but the treating physician attributed the patient's death to disease progression.

Table 75: FDA Analysis of Neurological Adverse Events in the Primary Safety Population

Primary Safety N=157 n, %				
	Any Grade	**Grade 3-4[a]**	**Serious**	**Fatal**
Nervous System Disorders (SOC) and Psychiatric Disorders (SOC)	65 (41)	7 (4)	10 (6)	1 (0.6)
Preferred Term				
Headache	21 (13)	1 (0.6)	0	0
Insomnia	15 (10)	1 (0.6)	0	0
Peripheral neuropathy and paresthesia	15 (10)	1 (0.6)	0	0

Primary Safety N=157 n, %				
Neurological changes[b]	14 (9)	1 (0.6)	3 (2)	1 (0.6)
Dizziness	7 (4)	0	0	0
Anxiety	4 (3)	0	0	0
Fatigue	3 (2)	0	0	0

Abbreviations: SOC, system organ class
[a] No Grade 4 AEs
[b] FDA grouped term that Includes ataxia (1 patient), cognitive disorder (1 patient), confusional state (1 patient), delirium (1 patient), loss of consciousness (1 patient), memory impairment (2 patients), mental status changes (3 patients), tremor (6 patients)
Source: FDA Analysis

Neurological Adverse Events resulting in Dose Delay or Treatment Discontinuation:
With the exception of neurological adverse events in 4 patients (3%), most events did not result in a dose delay or discontinuation. Three patients required a dose delay due to acute polyneuropathy, worsening baseline hydrocephalus, or a transient ischemic attack. One patient discontinued treatment due to worsening chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS), which was present prior to study treatment. Additional details on the 4 cases of treatment delay or discontinuation are discussed below:

- Treatment delay: 3 patients
  - *Patient* (b) (6): 74 year-old female with Stage IV de novo DLBCL who had a treatment delay on Day 22 following Grade 3 Acute Polyneuropathy. Per the patient narrative, the patient had a history of prior acute polyneuropathy but severity was not provided. On day 22 after 4 doses of epcoritamab, the patient endorsed numbness in her fingers and an electroneuromyography confirmed acute polyneuropathy. Treatment was delayed until Day 42 and her symptoms improved following treatment with prednisolone and IVIG. Although the patient had acute polyneuropathy prior to starting treatment with epcoritamab, it is unclear if treatment with the study drug contributed to its recurrence or increase in severity that necessitated intervention and delay of study treatment.
  - *Patient* (b) (6): 59 year-old female with Stage IV transformed DLBCL and a history of ongoing Grade 1 hydrocephalus prior to study therapy experienced worsening hydrocephalus (Grade 3), resulting in a dose delay on Day 323 of therapy. Patient presented with walking impairment, requiring a wheelchair, and imaging results consistent with worsening hydrocephalus in the

context of a complete response per Lugano classification. Therapy was delayed until Day 360. Although there is a temporal relationship between the treatment with epcoritamab and worsening of the hydrocephalus, the mechanism is less clear, especially in light of the pre-existing hydrocephalus of unclear etiology per narrative and the delayed onset of the event during therapy.

- *Patient* (b) (6): 83 year-old female with Stage IIE de novo DLBCL who experienced a dose delay on Day 21 until Day 29 following a Grade 1 transient ischemic attack. Patient tolerated 3 prior doses of epcoritamab (0.16 mg, 0.8mg, 48 mg). Prior to the 4th dose, the patient developed expressive aphasia and a left facial droop while at home. By the time she reached the emergency department, her symptoms had resolved. Imaging (CT and MRI) did not reveal an acute intracranial process. However, a CT angiogram of the head and carotid revealed mild to moderate stenosis in the proximal left internal carotid artery, left common carotid artery, and left subclavian artery. It is this reviewer's impression that the 3 preceding doses of epcoritamab treatment are unlikely to have acutely caused stenosis of the intracranial vasculature.

- Treatment discontinuation: 1 patient
  - *Patient* (b) (6): 54 year-old male with Stage IV de novo DLBCL and a history of Grade 1 CLIPPERs prior to study treatment who discontinued epcoritamab therapy following worsening of CLIPPERS to grade 3 on Day 78. Patient developed a Grade 1 headache after Day 65 dose of 48 mg of epcoritamab (Cycle 3 Day 8). A head MRI on Day 77 revealed a new hyperintense signal within the central pons, which was initially assessed as most likely toxic/metabolic in etiology. The subsequent day (Day 78), the patient presented with confusion, short term memory loss, ataxia. Word finding difficult, reduced facial/arm/leg sensation, left arm tremor, and continued headache. Diagnosed with Grade 3 CLIPPERS. His symptoms improved to Grade 2 with methylprednisolone. Developed progressive disease confirmed by PET/CT on Day 105. Whether epcoritamab may have contributed to worsening of the Grade 1 CLIPPERS is unclear given the temporal relationship and immune stimulating mechanism of action.

Given the low incidence of serious and/or severe neurological adverse events and the nature and context of those events that did occur, the monitoring and management as proposed by the Applicant appear appropriate at this time.

8.2.5.6 Cytopenia Events

Data:

Cytopenia events were evaluated based on grouped terms of neutropenia (PTs of neutropenia

and neutrophil count decreased), febrile neutropenia (same PT), thrombocytopenia (Standardized MedDRA Query of hematopoietic thrombocytopenia narrow search), and anemia (PTs of anemia, red blood cell count decreased, hemoglobin decreased, serum ferritin decreased, and hematocrit decreased).
In the Safety Pool 01 LBCL group, a total of 47 (28.1%) subjects had ≥1 neutropenia event (grouped term), and 36 of the 47 subjects had ≥1 grade 3 or 4 neutropenia event. Twenty-five (15.0%) subjects had neutropenia that was treated with G-CSF. Seven (4.2%) subjects experienced epcoritamab dose delays due to events of neutropenia.
Febrile neutropenia was experienced by only 4 (2.4%) subjects, with a maximum severity of grade 3 in 3 (1.8%) subjects and grade 4 in 1 (0.6%) subject. Febrile neutropenia resolved in all 4 subjects following treatment with G-CSF.
The incidence of neutropenia ranged from 10% to 20% across the Week≤8, Week 8 to ≤12, and Week 12 to ≤36 time periods, while the incidences of thrombocytopenia and anemia decreased to <4% after Week 8. No subjects in the Safety Pool 01 LBCL group discontinued treatment due to a TEAE of any cytopenia.
Thrombocytopenia and anemia events mainly occurred during the first 8 weeks, whereas incidence of neutropenia events was more evenly distributed across the first 36 weeks, although it should be noted that the interval durations varied.

The Applicant's Position:
The most frequent cytopenia event was neutropenia (neutropenia/neutrophil count decreased). Neutropenia is a well-known AE for anti-CD20 antibodies and has been observed in subjects who received epcoritamab therapy. Neutropenia events in the epcoritamab trials were managed by dose delays and/or treatment with G-CSF when indicated (15.0%, 25 subjects). No subjects discontinued treatment because of a neutropenia or other cytopenia events.

The FDA's Assessment:
FDA analysis of cytopenias by preferred term and by laboratory abnormality are shown in Table 76 and Table 77, respectively. In general, the FDA analysis is similar with the data presented by the Applicant regarding incidence of neutropenia. The FDA concurs that neutropenia was the most common cytopenia reported and that no cytopenia resulted in discontinuation of treatment. The FDA analysis also revealed that 13 patients (8%) delayed treatment due to a cytopenia, which was most commonly neutropenia.

Of note, the incidences of all cytopenias, regardless of grade, were significantly higher based on the laboratory dataset versus the AE reporting. Thus, the USPI will include incidences of the cytopenias based on the laboratory dataset. Additionally, given the incidence of treatment-emergent Grade 3 to 4 neutropenia and thrombocytopenia, the FDA will also propose inclusion of a Warning and Precaution for cytopenias .

Table 76: FDA Analysis of Cytopenias by Adverse Event Reporting in the Primary Safety Population

Primary Safety N=157 n, %			
Cytopenia	**Any Grade**	**Grade 3-4**	**Serious**
Any Cytopenia[a]	68 (43)	51 (32)	7 (4)
Preferred Term			
Neutropenia	44 (28)	33 (21)	1 (0.6)
Anemia	28 (18)	16 (10)	1 (0.6)
Thrombocytopenia	24 (15)	11 (7)	1 (0.6)
Lymphopenia	10 (6)	8 (5)	1 (0.6)
Leukopenia	7 (4)	5 (3)	1 (0.6)
Febrile neutropenia[b]	4 (3)	4 (3)	4 (3)

[a] Includes number and percentage of patients with any of the following based on preferred term and not laboratory value: anemia, febrile neutropenia, leukopenia, lymphopenia, neutropenia, and/or thrombocytopenia
[b] Same patient may be characterized as having neutropenia and febrile neutropenia
Source: FDA Analysis

Table 77: FDA Summary of Hematology Laboratory Abnormalities in the Primary Safety Population

Hematologic Laboratory Abnormality	Primary Safety Population		
	Sample Size[a]	All Grades n (%)	Grade 3 or 4[b] n (%)
Decreased Lymphocytes	146	124 (85)	113 (77)
Decreased Hemoglobin	153	95 (52)	19 (12)
Decreased Leukocytes	153	81 (53)	34 (22)
Decreased Neutrophils	148	74 (50)	47 (32)
Decreased Platelets	153	74 (48)	19 (12)

[a] Number of patients with a baseline and at least one post-baseline assessment for lab parameter
[b] Includes shifts from NCI CTCAE Grade <3 to ≥3 and shifts from Grade 3 to Grade 4
Source: FDA Analysis

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

Data:
N/A

The Applicant's Position:
No COA analyses informing safety/tolerability were conducted. COA analyses informing efficacy are discussed in Section 8.1.2.

The FDA's Assessment:
FDA notes that patient-reported outcomes (PROs) consisted of evaluation of health-related quality of life (HRQoL) using the FACT-Lym questionnaire subscales, FACT-LymS, VAS, and EQ-5D-3L. Based on the limited ability to interpret PROs in a single arm trial, FDA considers the results of these evaluations to be exploratory. Refer to the FDA Assessment under Efficacy Results—Secondary or Exploratory COA (PRO) Endpoints.

8.2.7. Safety Analyses by Demographic Subgroups

Data:
The following safety analyses by subgroup are presented for the Safety Pool 01 LBCL group. Due to the small sample sizes in some subgroups, differences in TEAEs incidences between groups should be interpreted with caution.
Age (<65, 65 to <75, ≥75):

There were no apparent age-related trends in the frequency and severity of events across TEAE categories and the AESIs of CRS, ICANS, and CTLS.

Sex:

In general, the frequency and severity of events were similar between female and male subjects across most TEAE categories. CTLS only occurred in male subjects (2 [1.2%] subjects). Differences in incidence ≥5% between females and male subjects, respectively, include:

- Fatal TEAEs: 1.6% vs 10.6%
- CRS (all grades): 60.3% vs 44.2%
- Serious TEAEs of CRS: 39.7% vs 26.2%
- Grade 3 or 4 CRS: 6.3% vs 0%
- ICANS: 9.5% vs 3.8%

Race:

In general, the frequency and severity of events were similar between race subgroups across TEAE categories and the AESIs of CTLS and ICANS. White subjects had a higher incidence of serious TEAEs compared to Asian and other subgroups (63.2% vs 50.0% and 48.4%, respectively). Higher frequencies of CRS (all grades) were noted in the Asian subgroup (63.3%) compared to the White or Other subgroups (51.9% and 32.3%, respectively); however, the differences were less for grade 3 CRS between the Asian subgroup (3.3%) and White or Other subgroups (2.8% and 0%, respectively), as were the incidences for serious TEAEs of CRS in the Asian (30.0%) subgroup and White or Other subgroups (32.1% and 29.0%, respectively). No subjects experienced grade 4 CRS.

- Despite any grade CRS being slightly higher in the Asian subgroup, grade 3 CRS incidence was similar between White and Asian subgroups. Exposure-safety analyses suggest that there is no apparent relationship between PK and CRS (any grade or grade 2 or higher).

Baseline Weight:

There were no apparent weight-related trends in the frequency and severity of events across TEAE categories and the AESIs of CRS, CTLS, and ICANS in the GCT3013-01 trial (Safety Pool 01). No weight-related trends were observed for CRS in the GCT3013-01 trial, CRS occurred in 50.0% of subjects in the <65 kg group, 55.1% of subjects in the 65 to <85kg group, and 43.2% of subjects in the >85 kg group.

Baseline Renal Function:

In general, the frequency and severity of events were similar across TEAE and AESI categories, with the exception of a trend towards higher incidence of serious TEAEs and any grade CRS that correlated with decreasing renal function. Differences in incidence ≥5% between the normal, mildly impaired, and moderately impaired renal function subgroups, respectively, include:

- Serious TEAEs: 52.9% vs 60.9% vs 68.0%
- CRS (all grades): 44.3% vs 55.1% (normal and mildly impaired, respectively)
- Serious cases of CRS 28.6%, vs 31.9% vs 40.0%.

There was no apparent renal function-related trend for Grade 3 or 4 CRS (4.3%, 1.5%, and 0%, respectively).

Baseline Hepatic Function:

In the Safety Pool 01 LBCL group (N=167), at baseline, the majority of subjects (79.0%) had normal hepatic function and 18.0% of subjects had mild hepatic dysfunction. In general, the frequency and severity of events were similar across TEAE and AESI categories with the possible exception of the following categories that had numerically higher incidences in the mild hepatic dysfunction group compared to the normal group:

- Serious TEAEs: 63.3% vs 57.6%
- TEAEs leading to dose delay: 43.3% vs 34.8%
- CRS (all grades):60.0% vs 49.2%
- Grade 3 or 4 CRS: 10.0% vs 0.8%
- ICANS (all grades): 13.3% vs 4.5%

Ann-Arbor Staging:

In the Safety Pool 01 LBCL group (N=167), approximately 3 times the number of subjects were Ann Arbor stage III/IV at baseline (125 subjects; 74.9%) compared to stage I/II at baseline (42 subjects; 25.1%). In general, the frequency and severity of events were similar across TEAE and AESI categories with exception of the following categories that had higher incidences (≥5%) in the Ann Arbor stage III/IV group compared to the normal group, respectively:

- Grade 3 and higher TEAEs: 64.8% vs 57.1%
- Serious TEAEs: 63.2% vs 42.9%
- TEAEs leading to dose delay: 37.6% vs 31.0%
- TEAEs leading to treatment discontinuation: 9.6% vs 2.4%
- Fatal TEAEs: 8.8% vs 2.4%
- CRS (all grades): 52.8% vs 42.9%
- ICANS (all grades): 8.0% vs 0%

Geographic Region:

In the Safety Pool 01 LBCL group (N=167), 15.0% of subjects were from North America, 55.7% from Europe, 16.2% from Asia, and 13.2% from other regions). The frequency and severity of events were generally similar between regions across all TEAE and AESI categories with the following exceptions:

- The use of dose delays for TEAE management was highest in Europe (44.1%) followed by other regions (36.4%), Asia (25.9%), and North America (16.0%).
- The incidence of grade 3 and higher TEAEs was >10% less in Asia (48.1%) than in Europe (66.7%), North America (60.0%), and other regions (68.2%).
- The incidence of serious TEAEs was >10% less in Asia (48.1%) than in Europe (61.3%) and other regions (59.1%).
- The incidence of CRS (all grades) was >10% higher in the Asian region (59.3%) than in Europe (48.4%) and North America (44.0%).

Prior Lines of Antilymphoma Therapy:

In the Safety Pool 01 LBCL group (N=167), 100 of 167 subjects (59.9%) received ≤3 lines of prior anti-lymphoma therapy and 67 (40.1%) of subjects received >3 lines. In general, the frequency and severity of events were generally similar between subgroups across TEAE categories and the AESIs of CRS and ICANS. CTLS was only observed in the ≤3 lines of prior anti-lymphoma

therapy subgroup (2.0%; 2 subjects). Differences in incidence ≥5% between subjects who received ≤3 lines of prior anti-lymphoma therapy compared to subjects who received >3 lines of prior anti-lymphoma therapy, respectively, include fatal TEAEs: 5.0% vs 10.4%

Prior Treatment with CAR-T:

In the Safety Pool 01 LBCL group (N=167),65 (38.9%) subjects received prior CAR-T cell therapy. In general, the frequency and severity of events were generally similar between subgroups across TEAE categories and the AESIs with the exceptions of differences in serious TEAEs, TEAEs leading to dose delay, and CRS. CTLS was only reported in subjects who did not have prior CAR-T cell therapy (2.0%; 2 subjects). Differences in incidence ≥5% between subjects who did not have prior CAR-T cell therapy compared to subjects who had prior CAR-T cell therapy, respectively, include:

- Serious TEAEs: 61.8% vs 52.3%
- TEAEs leading to dose delay: 39.2% vs 30.8%
- CRS (all grades): 58.8% vs 36.9%

Smaller differences were observed for grade 3 or 4 CRS (2.9% vs 1.5%, respectively).

The Applicant's Position:

Safety profiles were similar based on weight, age, or prior lines of anti-lymphoma therapy. Overall CRS rates were approximately 10 to 20% higher between subgroups in each category for female subjects, Asian subjects, subjects treated in Asia (geographic region), and in subjects without prior CAR T-cell therapy, but rates of grade 3 or 4 CRS were similar between subgroups. Subjects with renal impairment (mild or moderate) or hepatic dysfunction (mild) at baseline, or who were Ann Arbor stage III/IV showed trends towards higher frequencies of serious TEAEs and CRS, compared to subjects with normal renal/hepatic function or who were Ann Arbor Stage I/II. These results may be confounded by the potential for increased disease severity for subjects in these subgroups, and the numerical difference must be interpreted with caution. The similarities in TEAE and AESI profiles compared to the overall population for subjects with >3 lines prior lymphoma treatment or with prior CAR T-cell therapy suggests that epcoritamab has a manageable safety profile even in these most heavily pretreated subjects.

The FDA's Assessment:

FDA's safety analysis based on age, sex, race, ethnicity, and number of prior lines of therapy subgroups is summarized below in Table 78 through Table 85. FDA reviewed the safety results based on baseline weight, renal function, hepatic function, region, Ann Arbor Staging, and prior CAR-T therapy exposure in the Applicant's CSR but did not independently verify those results. The trend of higher incidences of serious TEAEs with more significant hepatic or renal impairment is not completely unexpected but given the low numbers of patients represented, the data is difficult to interpret. Other findings, such as the higher incidence of serious, severe, fatal TEAES or those requiring modification in patients with Stage III/IV disease is also not completely unexpected given the more advanced stage of disease. Other smaller differences in subgroups are of unclear clinical significance.

FDA agrees that there are no significant clinical differences in the rates of TEAEs, including CRS, ICANS, infections, and cytopenias across the main subgroups examined. However, the numbers of patients in certain subgroups, particularly in the age ≥75 years subgroup and most racial subgroups, are too small to draw any conclusions. Additionally, in some categories like ICANS and even fatal AEs, the number of events is overall low and, thus, difficult to interpret differences between subgroups.

For potential age-related differences, the USPI will state that there were no clinically meaningful differences observed between patients ≥65 years of age compared to younger patients and will cite the number and percentage of patients in the 65 to <75 year and ≥75 years subgroups. For race and ethnicity, the primary safety population lacked diversity with most patients being either White or Asian. No Black or African American or Hispanic or Latino patients were enrolled as reported. Inclusion of an overall diverse population was also not present when examining the demographics of the larger supportive safety population (Table 46). Thus, the FDA will issue a PMC requesting that the Applicant conduct an integrated analysis of data from clinical trials to further characterize the safety, efficacy, pharmacokinetics, and pharmacodynamics of epcoritamab monotherapy among U.S. racial and ethnic minority patients with LBCL.

Table 78: FDA analysis of Age Subgroups

Age Subgroup	Primary Safety Population N = 157 n (%)
< 65 years	80 (51)
65 to < 75 years	48 (31)
≥75 years	29 (18)
Source: FDA analysis	

Table 79: FDA Summary of Adverse Events by Age

Adverse Event Category	Age <65 years N = 80 n (%)	Age 65 to <75 years N = 48 n (%)	Age ≥75 years N = 29 n (%)
All Grade TEAEs	80 (100)	47 (98)	29 (100)
Grade 3 or 4 TEAEs	52 (65)	25 (52)	16 (55)
Serious TEAEs	49 (61)	24 (50)	16 (55)
Fatal TEAEs	5 (6)	4 (8)	0
CRS per ASTCT (All Grades)	37 (46)	28 (58)	13 (45)
Cytopenias (All Grades)	38 (48)	14 (29)	12 (41)
ICANS (All Grades)	5 (6)	3 (6)	2 (7)
Infections (All Grades)	40 (50)	19 (40)	12 (41)
Abbreviations: TEAE, treatment emergent adverse event Source: FDA analysis			

Table 80: FDA Analysis of Sex Subgroups

Sex Subgroup	Primary Safety Population N = 157 n (%)
Male	94 (60)
Female	63 (40)
Source: FDA analysis	

Table 81: FDA Summary of Adverse Events by Sex Subgroup

Adverse Event Category	Male N = 94 n (%)	Female N = 63 n (%)
All Grade TEAEs	93 (99)	63 (100)
Grade 3 or 4 TEAEs	55 (59)	38 (60)
Serious TEAEs	51 (54)	38 (60)
Fatal TEAEs	8 (9)	1 (2)
CRS (All Grades)	40 (43)	38 (60)
Cytopenias (All Grades)	31 (33)	33 (52)

Adverse Event Category	Male N = 94 n (%)	Female N = 63 n (%)
ICANS (All Grades)	4 (4)	6 (10)
Infections (All Grades)	44 (47)	27 (43)
Abbreviations: TEAE, treatment emergent adverse event Source: FDA analysis		

Table 82: FDA Analysis of Race and Ethnicity Subgroups

Race/Ethnicity	Primary Safety Population N = 157 n (%)
White	96 (61)
Black or African American	0
Asian	30 (19)
Native Hawaiian or Pacific Islander	1 (0.6)
American Indian or Alaska Native	0
Other	6 (4)
Hispanic or Latino	0
Not reported race	24 (15)
Not reported ethnicity	133 (85)
Source: FDA analysis	

Table 83: FDA Analysis of Adverse Events by White and Asian Race Subgroups

Adverse Event Category	White N = 96 n (%)	Asian N = 30 n (%)
All Grade TEAEs	96 (100)	29 (97)
Grade 3 or 4 TEAEs	62 (66)	14 (47)
Serious TEAEs	59 (61)	15 (50)
Fatal TEAEs	6 (6)	1 (3)
CRS (All Grades)	49 (51)	19 (63)
Cytopenias (All Grades)	40 (42)	11 (37)
ICANS (All Grades)	8 (8)	1 (3)
Infections (All Grades)	46 (48)	7 (23)
Abbreviations: TEAE, treatment emergent adverse event Source: FDA analysis		

Table 84: FDA Analysis of Prior Lines of Therapy Subgroups

Lines of Prior Therapy	Primary Safety Population N = 157 n (%)
Less than or equal to 3 lines	96 (61)
Greater than 3 lines	61(39)
Source: FDA analysis	

Table 85: FDA Analysis of Adverse Events by Prior Lines of Therapy

Adverse Event Category	≤3 lines N = 96 n (%)	>3 lines N = 61 n (%)
All Grade TEAEs	95 (99)	61 (100)
Grade 3 or 4 TEAEs	59 (61)	34 (56)
Serious TEAEs	57 (59)	32 (52)
Fatal TEAEs	4 (4)	5 (8)
CRS (All Grades)	50 (52)	28 (46)
Cytopenias (All Grades)	38 (40)	26 (43)
ICANS (All Grades)	7 (7)	3 (5)
Infections (All Grades)	39 (41)	32 (52)
Abbreviations: TEAE, treatment emergent adverse event Source: FDA analysis		

8.2.8. Specific Safety Studies/Clinical Trials

Data:
N/A

The Applicant's Position:
N/A

The FDA's Assessment:
Not applicable

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

Data:
N/A

The Applicant's Position:
No carcinogenicity studies have been conducted with epcoritamab.

The FDA's Assessment:
The FDA agrees with the Applicant's position. Refer to Section 5.5.3 on Carcinogenicity.

Human Reproduction and Pregnancy

Data:
Epcoritamab has the potential to be transmitted from the mother to the developing fetus, by its binding to FcRn. Fetal exposure to epcoritamab may cause adverse outcomes including B-cell lymphocytopenia and alterations in normal immune responses in infants exposed in-utero, which are reversible.
Epcoritamab has not been assessed in subjects with reproductive potential who are attempting to conceive. No pregnant subjects are known to have received epcoritamab in clinical trials. No clinical data is available regarding use of epcoritamab during human pregnancy.
Consistent with ICH S9 for the development of oncology therapies, fertility and early embryonic studies were not conducted with epcoritamab.

The Applicant's Position:
Females of reproductive potential should use effective contraception during treatment with epcoritamab and for at least 6 months after the last dose.

The FDA's Assessment:
Refer to FDA assessment in Section 5.5.4 Reproductive and Developmental Toxicology.

Pediatrics and Assessment of Effects on Growth

Data:
N/A

The Applicant's Position:
Epcoritamab has not been assessed in children. The Agreed iPSP, dated 15 Dec 2021, includes a waiver for the condition of mature B cell lymphoma in patients <1 year and a deferral in patients ≥1 to 18 years for the completion of the population PK modeling study.

The FDA's Assessment:
The FDA agrees with the Applicant's position. Epcoritamab has not been evaluated in a

pediatric population and none of the studies in support of this application have enrollment of patients from a pediatric population. The Applicant has an agreed iPSP on file as stated above. A PMR will be issued pertaining to characterizing the safety and efficacy of epcoritamab in a pediatric population.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Data:

All doses of epcoritamab have been administered subcutaneously at clinical sites by trained clinical trial staff. As of the 31 Jan 2022 data cut-off date, 4 cases of medication errors have been reported in the program of which 3 were overdoses but these subjects did not receive epcoritamab doses greater than 48 mg and they were not patients in the GCT3013-01 or GCT3013-04 Expansion Parts. Only 1 subject reported non-serious chills and headache for which no treatment was required. Neither the effects of overdose of epcoritamab nor an antidote to overdose are known.

In dose escalation, 3 subjects received a full planned dose of 60 mg with no unexpected adverse effects.

The Applicant's Position:

In the event of overdose, subjects should be monitored for any signs or symptoms of adverse reactions with administration of appropriate supportive treatment. It does not have addictive properties. The potential for misuse for illegal purposes is low. Withdrawal and rebound are not applicable.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Data:

Not applicable, as epcoritamab is not currently registered or approved in the U.S. or any other part of the world.

The Applicant's Position:

N/A

The FDA's Assessment:

As epcoritamab is not currently registered or approved in the U.S. or any other part of the world, there is no postmarketing experience to date.

Expectations on Safety in the Postmarket Setting

Data:
Toxicities have been adequately represented in the studies included in this application.

The Applicant's Position:
Routine pharmacovigilance will be conducted in the postmarket setting to monitor for adverse events.

The FDA's Assessment:
Given the limited data with long-term exposure with epcoritamab, the FDA will issue a postmarketing requirement requesting continued collection and a comprehensive analysis of safety of epcoritamab administration. The primary safety concerns that have been identified are cytokine release syndrome, immune effector cell-associated neurotoxicity syndrome, hematologic toxicity, and infections.

8.2.11. Integrated Assessment of Safety

Data:
Epcoritamab was administered as a SC injection in 28-day (4-week) cycles. The core safety analysis is based on the pivotal GCT3013-01 trial, which provides the largest LBCL population from a single trial (Safety Pool 01 LBCL group; N=167). The median number of cycles of treatment initiated per subject was 5.0 (range 1, 22), and the median duration of treatment was 3.7 months (range: 0, 20). A total of 53 (31.7%) subjects continued to receive epcoritamab treatment as of the data cutoff date of 31 Jan 2022. Exposure is considered adequate to support the evaluation of safety of the proposed dosing regimen for the target indication.
The TEAEs observed were consistent with those expected for a bispecific CD3/CD20-directed T cell engager. The most common (≥20%) TEAEs of any grade included CRS (50.3%), fatigue (24.6%), pyrexia (22.8%), injection-site reaction (22.2%), neutropenia (22.2%), and nausea (20.4%). The worst severity for most individual PTs (event-level analysis) was grade 1 or 2 (except for cytopenias), and most events occurred with highest frequency during the first 8 weeks of treatment.
Grade 3 or higher TEAEs were reported in 62.9% subjects. Grade 3 or 4 TEAEs reported in ≥5% of subjects were hematological and included neutropenia (15.6%), anemia (10.2%), neutrophil count decreased (6.0%), and thrombocytopenia (6.0%). Cytopenias (eg, neutropenia, anemia, thrombocytopenia) were generally managed through dose delay and/or treatment with G-CSF for neutropenia (grouped term neutropenia or neutrophil count decreased), which was administered to 15.0% of subjects. No subjects discontinued epcoritamab treatment due to cytopenia.
Serious TEAEs were reported in 58.1% of subjects. Serious TEAEs experienced by ≥2% of subjects included CRS (31.1%); pleural effusion (4.8%); febrile neutropenia, ICANS, pneumonia, pyrexia, and sepsis (2.4% each).
Fatal (grade 5) TEAEs were reported for 12 (7.2%) subjects, 11 of which were considered

unrelated to epcoritamab by the investigator. One subject had a fatal (grade 5) TEAE that was considered related by the investigator (ICANS in the context of disease progression). Overall, a total of 68 (40.7%) subjects with LBCL died during the trial: 37 subjects during the treatment period and 31 subjects during follow-up. Disease progression (32.3%; 54 subjects) was the primary cause of most deaths.

TEAEs led to treatment discontinuation in 13 (7.8%) subjects. TEAEs leading to treatment discontinuation reported in more than 1 subject included COVID-19, COVID-19 pneumonia, and MDS: 2 (1.2%) subjects each. TEAEs leading to treatment discontinuation considered related to epcoritamab by the investigator were recorded for 1 (0.6%) subject each: CRS, ICANS, and CLIPPERS.

Based upon the activity of epcoritamab as a bispecific T-cell engager, CRS, ICANS, and CTLS were considered AESIs. Taking into consideration the anticipated risk of CRS, precautions to minimize the incidence and severity of CRS were implemented in the GCT3013-01 trial including guidelines on management, premedication, prophylactic corticosteroids, hospitalizations, and monitoring. Over the course of the trial, instructions for CRS and ICANS management according to the protocol have evolved based on the data observed to date and availability of new guidelines.

CRS was the most frequent TEAE, experienced by 84 (50.3%) subjects. Almost all subjects (80 out of 84 subjects) experienced a maximum grade 1 or 2 event and there were no grade 4 or 5 cases reported in LBCL subjects. The majority of subjects (68 out of 84 subjects) had an event during the first cycle of treatment after the initial full 48 mg dose on C1D15, with median onset of 19.9 hours following administration of the C1D15 dose. Median time to resolution was 2.0 days (range: 1, 27). All cases of CRS resolved except for 2 subjects whose CRS occurred in the setting of disease progression and were ongoing at the time of the subject's death. Only one subject (0.6%) had a CRS (grade 1) event that led to treatment discontinuation.

ICANS occurred in 10 (6.0%) subjects, most cases (9 out of 10 subjects) were grade 1 or 2, and the median time to onset was 16.5 days, which correlates with the timing of the first full 48 mg dose on C1D15. Seven of the cases were concurrent with CRS events. One (0.6%) subject had a fatal (grade 5) ICANS event that was considered related to epcoritamab by the investigator and occurred in a subject with several confounding conditions including disease progression. All other episodes resolved with a median time to resolution of 5.0 days.

CTLS occurred in 2 (1.2%) subjects. Both events were grade 3, and in both subjects the CTLS events occurred in the setting of disease progression and were unresolved at time of subject death. The primary cause of death was disease progression for both subjects.

Serious TEAEs of infection were reported in 27 (16.2%) subjects; the most frequently reported serious infections included pneumonia and sepsis in 4 (2.4%) subjects each and COVID-19, COVID-19 pneumonia, and cellulitis in 3 (1.8%) subjects each. Serious TEAEs of infection considered epcoritamab related by the investigator included sepsis, upper respiratory tract infection, and oral herpes in 1 (0.6%) subject each.

Neutropenia events (grouped term neutropenia and decreased neutrophil count) were reported in 47 (28.1%) subjects, with 36 subjects experiencing grade 3 or 4 events. Neutropenia

was managed with G-CSF (15.0%) and/or dose delays (4.2%). No subjects discontinued epcoritamab treatment due to a TEAE of neutropenia. Febrile neutropenia was reported in 4 (2.4%) subjects (grade 3, n=3; grade 4, n=1); all 4 subjects' events resolved with G-CSF treatment. The incidence of neutropenia events (grouped term + febrile neutropenia) was ≥12.5% through the Week 12 to ≤36 period.
Injection site reactions were experienced by 29.9% of LBCL subjects in Safety Pool 01, and all were grade 1 or 2 in severity.

The Applicant's Position:
Overall, the safety profile of epcoritamab monotherapy at the proposed 48 mg dosing regimen is considered manageable with appropriate monitoring and mitigation measures in adult patients with R/R (D)LBCL after 2 or more lines of systemic therapy.

The FDA's Assessment:
In general, the FDA agrees with the Applicant's position. The safety data support that epcoritamab demonstrated a tolerable safety profile in patients with relapsed or refractory LBCL.

The safety profile of epcoritamab was primarily supported by analysis of 157 patients with R/R LBCL that received the recommended dose and regimen. The median duration of treatment was 5 cycles (range 1 to 20), with 69% exposed for at least 9 cycles. The most common adverse events (≥20%) were cytokine release syndrome (51%), fatigue (29%), administration related reactions (28%), musculoskeletal pain (28%), neutropenia (28%), fever (24%), abdominal pain (23%), diarrhea (20%), and nausea (20%). The most common Grade 3 to 4 laboratory abnormalities (≥ 10%) were decreased lymphocyte count (77%), decreased neutrophil count (32%), decreased leukocyte count (22%), decreased hemoglobin (12%), and decreased platelet count (12%). Serious adverse events occurred in 57%, most often due to CRS (29%); sepsis (9%)/ pleural effusion (5%); 3% each of COVID-19, febrile neutropenia, fever, ICANS, renal insufficiency and urinary tract infection; and 2% each of cellulitis, pneumonia, and upper respiratory tract infection. Adverse events leading to treatment interruption occurred in 34%, most often due to CRS, neutropenia, and infection. Adverse events leading to treatment discontinuation occurred in 8%, most often due to infection, particularly COVID-19. Thus, the primary safety issues identified with epcoritamab include CRS, ICANS, infections, and cytopenias.

Based on the FDA's evaluation of the data, the USPI will need to include a Boxed Warning for CRS and ICANS and Warning and Precaution sections for infections and cytopenias.

SUMMARY AND CONCLUSIONS

8.3. Statistical Issues

The FDA's Assessment:

Efficacy

The efficacy of epcoritamab monotherapy is based primarily on the results from GCT3013-01, an open-label, multi-cohort, multicenter, single-arm trial in 157 patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy. The efficacy was supported by GCT3013-04, an open-label, single-country, interventional, multicohort, phase 1/2 trial in 36 Japanese patients with R/R B-NHL.

Efficacy was established on the basis of overall response rate determined by Lugano 2014 criteria as assessed by Independent Review Committee and duration of response from Study GCT3013-01. Among the 157 patients, the ORR per IRC was 63% (95% CI: 55, 71), with 39% (95% CI: 31, 47) achieving best response of CR. With a median follow-up for DOR of 10.7 months, the estimated median DOR was 12.0 months (95% CI: 6.6, not reached). In all responders with LBCL, with an estimated approximately 60% remaining in response at 6 and 9 months.

Efficacy was supported by Study GCT3013-04. Among the 36 Japanese patients, the ORR per IRC was 56% (95% CI: 38, 72), with 44% achieving best response of CR.

Given both studies GCT3013-01 and GCT3013-04 were open-label and single-arm studies, there are inherent limitations in interpreting the study data and Applicant's analyses results. For example

- Analyses for time-to-event endpoints are not interpretable in a single arm study due to lack of comparator arm. FDA considers such endpoints exploratory and not adequate to be used as measures of efficacy in single-arm trials intended to support approval.
- A 35% ORR rate was chosen to compare with ORR rates obtained in GCT3013-01 and GCT3013-04 studies. The use of this 35% control rate from historical trials to assess whether the observed treatment effect represents an improvement over available therapy is challenging. There can be differences across trials (e.g., in design, conduct, response assessment intervals, study population, etc.) which may or may not be easily discernible and which could lead to erroneous conclusions regarding observed differences in the response estimate between the investigational arm and a historical control (e.g., erroneously attributing differences in response rate to the investigational drug). Thus, the null hypothesis of 35% was only used to inform the sample size for the two studies respectively.

8.4. Conclusions and Recommendations

The FDA's Assessment:

The benefit-risk assessment is favorable for epcoritamab, a bispecific CD20 directed CD3 T cell engager indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma, not otherwise specified, including DLBCL arising from indolent lymphoma, and high-grade B-cell lymphoma, after two or more lines of systemic therapy

Efficacy:

Efficacy of epcoritamab is based on the results from the aggressive NHL expansion cohort in Study GCT3013-01, an open-label, multicenter, multicohort study, which included 157 patients with relapsed or refractory large B-cell lymphoma who had received at least two prior therapies, including an anti-CD20 monoclonal antibody.

Patients received epcoritamab subcutaneously in 28-day cycles, at step-up dosing in Cycle 1 (0.16 mg on Day 1, 0.8 mg on Day 8, and 48 mg on Day 15 and Day 22), 48 mg weekly in Cycles 2-4, 48 mg every other week in Cycles 5-9, and 48 mg every four weeks from Cycles 10 onwards. Epcoritamab was administered until progressive disease or unacceptable toxicity.

Efficacy was established on the basis of objective response rate and duration of response as assessed by an independent review committee according to Lugano criteria (Cheson et al, 2014). Among the 157 patients, the ORR per IRC was 63% (95% CI: 55, 71), with 39% achieving a complete response. With a median follow-up for DOR of 9.8 months, the estimated median DOR was 15.5 months (95% CI: 9.7, not reached). Of the 99 responders, 61% remained in response at 9 months and 55% at 12 months.

Safety:

The safety profile of epcoritamab was primarily supported by analysis of 157 patients with R/R LBCL that received the recommended dose and regimen. The median duration of treatment was 5 cycles (range 1 to 20), with 69% exposed for at least 9 cycles. The most common adverse events (≥20%) were cytokine release syndrome (51%), fatigue (29%), administration related reactions (28%), musculoskeletal pain (28%), neutropenia (28%), fever (24%), abdominal pain (23%), diarrhea (20%), and nausea (20%). The most common Grade 3 to 4 laboratory abnormalities (≥ 10%) were decreased lymphocyte count (77%), decreased neutrophil count (32%), decreased leukocyte count (22%), decreased hemoglobin (12%), and decreased platelet count (12%). Serious adverse events occurred in 57%, most often due to CRS (29%); sepsis (9%)/ pleural effusion (5%); 3% each of COVID-19, febrile neutropenia, fever, ICANS, renal insufficiency and urinary tract infection; and 2% each of cellulitis, pneumonia, and upper respiratory tract infection. Adverse events leading to treatment interruption occurred in 34%, most often due to CRS, neutropenia, and infection. Adverse events leading to treatment discontinuation occurred in 8%, most often due to infection, particularly COVID-19. Thus, the primary safety issues identified with epcoritamab include CRS, ICANS, infections, and cytopenias.

Benefit-Risk:

Epcoritamab has an overall favorable benefit-risk in patients with relapsed or refractory large B-cell lymphoma, including DLBCL, not otherwise specific, DLBCL arising from indolent lymphoma and HGBCL after two or more lines of systemic therapy. In the 157 patients with relapsed or refractory LBCL enrolled in the GCT 3013-01 study, the median age was 64 years (range: 20 to 83 years), 49% were 65 years of age or older, 60% were male, 61% were White, 19% were Asian, 0.6% were Native Hawaiian or Pacific Islander and none were Black or African American, or Hispanic or Latino. A total of 75% of patients had Stage III-IV disease and 97% of patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. The median number of prior therapies was 3 (range: 2 to 11), with 29% receiving 2 prior therapies, 32% receiving 3 prior therapies, and 39% receiving more than 3 prior therapies.

In this population, the overall response rate of 63%, with 39% achieving complete response, with durability and a tolerable safety profile constitutes a meaningful clinical benefit and a favorable benefit-risk evaluation. To support accelerated approval, the efficacy data are considered in the context of available therapy for patients with relapsed or refractory large B-cell lymphoma in the 3rd line setting and beyond. Available therapy includes chemoimmunotherapy options such as bendamustine plus rituximab (BR), gemcitabine or gemcitabine and oxaliplatin (GemOx) with or without rituximab. Additionally, polatuzumab vedotin plus BR or CAR T-cell therapy are available therapies in this setting. In the 3rd line setting and beyond, the ORRs for the chemoimmunotherapy options range from 25% to 38% with associated durability. Polatuzumab vedotin in combination with BR demonstrated an ORR of 63% with durability. Treatment with CAR T-cell therapy options yield high overall response rates and associated durability ranging from 50-73% and median DORs between 9.2 months and 16.7 months. However, CAR T-cell therapy represents a distinct therapeutic modality and these options may be limited due to eligibility and accessibility reasons. Of the 157 patients with R/R LBCL treated with epcoritamab, 71% had received 3 or more prior lines of systemic therapy, 39% received prior CAR T-cell therapy, 20% with prior autologous stem cell transplant, and 11% with prior polatuzumab vedotin. Therefore, the overall response of 63% with associated durability with epcoritamab provides data to support a clinically meaningful benefit in the context of available therapy for patients with relapsed or refractory large B-cell lymphoma in the 3rd line setting and beyond.

Given that the primary efficacy population consisted of 81% DLBCL (including 25% with DLBCL arising from indolent lymphoma), 13% high-grade B-cell lymphoma, and a limited number of patients with primary mediastinal B-cell lymphoma and follicular lymphoma Grade 3B (3% each), (b) (4) (b) (4) the efficacy data for epcoritamab demonstrates substantial evidence of effectiveness in support of accelerated approval for the following indication:

- *Treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), not otherwise specified, including DLBCL arising from indolent lymphoma, and high-grade B-cell lymphoma, after two or more lines of systemic therapy*

Confirmatory Trial

The Applicant has an ongoing randomized trial in patients with relapsed or refractory diffuse large B-cell lymphoma. Study GCT3013-05 is an open-label, multicenter, randomized (1:1) trial evaluating epcoritamab monotherapy compared to investigator's choice chemotherapy of either R-GemOx or BR in approximately 480 patients with relapsed or refractory diffuse large B-cell lymphoma following at least 1 prior line of therapy and who have failed or are ineligible for autologous SCT. The primary endpoint is overall survival. The secondary endpoints include independent review committee and investigator-assessed progression-free survival, overall response rate, complete response rate, duration of response, time to response, and rate and duration of MRD negative status. Additional secondary efficacy endpoints will also include investigator assessment of above parameters by LYRIC criteria.

As of March 30, 2023, 475 patients have been enrolled out of the planned 480 patients. The FDA considers this ongoing trial to be supportive of accelerated approval for the indication described above. A PMR will be issued based on this trial to verify and describe the clinical benefit of epcoritamab in patients with relapsed or refractory large B-cell lymphoma (Section 13).

X	X
Primary Statistical Reviewer	Statistical Team Leader
X	X
Nicole Sunseri, MD PhD Primary Clinical Reviewer	Nicholas Richardson, DO, MPH Clinical Team Leader

9 Advisory Committee Meeting and Other External Consultations

The FDA's Assessment:

This application was not presented to the Oncologic Drugs Advisory Committee or other external consultations because the application did not raise significant efficacy or safety issues for the recommended indication.

10 Pediatrics

The Applicant's Position:

The Agreed iPSP, dated 15 Dec 2021, includes a waiver for the condition of mature B cell lymphoma in patients <1 year and a deferral in patients ≥1 to 18 years for the completion of the population PK modeling study.

The FDA's Assessment:

The FDA agrees with the Applicant's position. A pediatric population was not included in any of the studies contained in this application. Efficacy is not established in the pediatric population. Refer to the Section 13 regarding a postmarketing requirement addressing studies in a pediatric population.

11 Labeling Recommendations

Data: The table below provides a high-level summary of the changes made by the FDA to the US Prescribing Information (USPI) for EPKINLY (epcoritamab-bysp) BLA 761324; see the USPI and Medication Guide attached to the approval letter for final labeling.

Section	Applicant's Proposed Labeling	FDA's proposed Labeling
Highlights of Prescribing Information		FDA modified this section to align with changes made in the full prescribing information.
Boxed Warning	N/A	FDA added a boxed warning for the risks of cytokine release syndrome (CRS) and immune effector cell-associated neurological toxicity syndrome (ICANS).
1 Indications and Usage	(b) (4)	FDA modified the indication as follows: Indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) not otherwise specified, including DLBCL arising from indolent lymphoma, and high-grade B-cell lymphoma, after two or more lines of systemic therapy.
2 Dosage and Administration	(b) (4) includes recommendations for premedication and prophylaxis for cytokine release syndrome (CRS) (b) (4) includes dose modifications and management for CRS and immune effector cell-associated neurological toxicity syndrome (ICANS) (b) (4) includes instructions for preparation	FDA added a new section 2.1 Important Dosing Information to highlight important points for safe administration of Epkinly, including adding a recommendation that patients be hospitalized for 24 hours after administration of the first 48 mg dose. In section 2.2, FDA simplified the dosing table and modified the instructions for restarting Epkinly after dosage delay (b) (4) (b) (4) The terms (b) (4) (b) (4) changed to refer to the actual dose itself. A new subsection 2.3 Restarting Epkinly after Dosage Delay was added to provide instructions for restarting.

		FDA added a recommendation for patients to be hospitalized for 24 hours after administration of the cycle 1, day 15 dosage of 48 mg. FDA added a new subsection (b) (4) for recommendations for antimicrobial prophylaxis. FDA modified subsection (b) (4) Dosage Modifications and Management of Adverse Reactions to align with language and management tables in other FDA-approved bi-specific T-cell engager antibody products.
5 Warning and Precautions (W&P)	Includes CRS, ICANS, serious infections, and (b) (4)	FDA modified this section to remove W&P for (b) (4) and to include additional W&P for cytopenias and embryofetal toxicity in addition to the W&P for CRS, ICANS, and infections.
6 Adverse Reactions	Summary text provided (b) (4) (b) (4)	FDA modified this section based on FDA review of safety data to align with regulations, guidances, and current labeling practices.
8 Use in Specific Populations	8.1 and 8.2 terminology and formatting consistent with current Pregnancy and Lactation Labeling Rule (PLLR) guidance and best labeling practices. 8.3 provides specific contraception instructions for females	FDA modified these sections to align with other products in the same class and recommendations in guidance.
11 Description		FDA generally agreed with the applicant's proposed language but modified this section to add the established pharmaceutical class and dosage form and to align with regulations and

		recommendations in guidance.
12 Clinical Pharmacology	Details provided on mechanism of action, pharmacodynamics, pharmacokinetics, and immunogenicity.	FDA modified this section to align with current labeling practice and guidance. Additions included: • Adding time course of circulation of B-cell and concentrations of cytokines • Adding a statement that PK parameters were evaluated at the approved recommended dosage and are presented as geometric mean (CV%) unless otherwise specified
14 Clinical Studies	Includes description of the design of the single-arm study GCT3013-01. Data presented on the patient population as well as primary and clinically relevant secondary endpoints are based on the 157 subjects with LBCL in this study.	FDA modified this section to include efficacy results for the indicated population (148) of DLBCL, NOS and high-grade B-cell lymphoma. FDA included median follow-up for responders in text below the efficacy table and added duration of response at 9 months. Any (b) (4) were removed.

The Applicant's Position:

The USPI for epcoritamab meets the regulatory requirements for providing a summary of the essential scientific information needed for its safe and effective use and is consistent with current FDA guidance and best labeling practices.

The FDA's Assessment:

FDA modified sections of the USPI as described in the table above. The Medication Guide was updated to align with changes made to the USPI.

12 Risk Evaluation and Mitigation Strategies (REMS)

The FDA's Assessment:

The Division of Risk Management (DRM) in the Office of Surveillance and Epidemiology (OSE) reviewed this Application and concurs with the review team that additional risk evaluation mitigation strategies (REMS) are not required for the safe use of epcoritamab in the indicated population.

13 Postmarketing Requirements and Commitments

The FDA's Assessment:

The review team recommends three postmarking requirements (PMR) and one postmarketing commitment. The PMRs consist of an accelerated approval PMR to verify clinical benefit, a safety PMR for further characterization of safety with longer-term use of epcoritamab, and a PMR addressing the need for characterization of safety and efficacy in a pediatric patient population. The PMC addresses the need to obtain additional safety, efficacy, pharmacokinetics, pharmacodynamic data for epcoritamab monotherapy in racial and ethnic minority patients, particularly those in the U.S.

Postmarking Requirements:

1. Complete a randomized clinical trial in patients with relapsed or refractory large B-cell lymphoma. The trial should compare epcoritamab monotherapy to an investigator's choice of standard therapies for patients with relapsed or refractory large B-cell lymphoma. The primary endpoint should be overall survival with secondary endpoints that include progression-free survival and response rate.

Trial Completion:	12/2024
Final Report Submission:	12/2025

2. Complete a clinical trial to confirm the appropriate dose of epcoritamab and to assess the safety, pharmacokinetics, and preliminary efficacy of epcoritamab monotherapy in pediatric patients with relapsed or refractory aggressive mature B-cell lymphoma.

Trial Completion:	11/2028
Final Report Submission:	05/2029

3. Conduct an integrated safety analysis of data from patients with large B-cell lymphoma and other lymphoid malignancies to further characterize the long-term incidence, severity, and outcome of the known serious risks of immune effector cell-associated neurotoxicity syndrome, neurologic toxicity, hematologic adverse events, and infections. Include a comprehensive analysis from all available data sources including but not limited to patient-level and pooled analyses of ongoing and completed clinical trials.

Draft Protocol Submission (Analysis Plan):	12/2024
Final Protocol Submission (Analysis Plan):	12/2025
Interim Report Submission:	12/2026
Trial Completion:	05/2028
Final Report Submission:	05/2029

Postmarketing Commitment:

1. Conduct an integrated analysis of data from clinical trials to further characterize the safety, efficacy, pharmacokinetics, and pharmacodynamics of epcoritamab monotherapy among U.S. racial and ethnic minority patients with large B-cell lymphoma. The population should be representative of the U.S. population, including racial and ethnic diversity, of patients with large B-cell lymphoma and allow for interpretation of the results in these populations.

Draft Protocol Submission (Analysis Plan):	06/2024
Final Protocol Submission (Analysis Plan):	06/2025
Study Completion:	02/2028
Final Report Submission:	08/2028

FDA PMC/PMR Checklist for Trial Diversity and U.S. Population Representativeness

The following were evaluated and considered as part of FDA's review:		Is a PMC/PMR needed? Yes
□	The patients enrolled in the clinical trial are representative of the racial, ethnic, and age diversity of the U.S. population for the proposed indication.	_X_ Yes __ No
□	Does the FDA review indicate uncertainties in the safety and/or efficacy findings by demographic factors (e.g. race, ethnicity, sex, age, etc.) to warrant further investigation as part of a PMR/PMC?	_X_ Yes __ No
□	Other considerations (e.g.: PK/PD), if applicable:	_X_ Yes __ No

14 Division Director (DHOT) (NME ONLY)

X

15 Division Director (OCP)

X

16 Division Director (OB)

X

17 Division Director (Clinical)

X

18 Office Director (or designated signatory authority)

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

X _____

19 Appendices

19.1. References

The Applicant's References:
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The FDA's References:
The FDA had no additional references.

19.2. Financial Disclosure

The Applicant's Position:
Financial disclosure information is provided in Section 8.1.2 for the pivotal aNHL cohort of the GCT3013-01 Trial

The FDA's Assessment:

The Applicant provided information regarding financial certification and disclosure is provided for the pivotal aNHL cohort of study GCT3013-01 entitled "A Phase 1/2, Open-Label, Dose-Escalation Trial of GEN3013 in Patients with Relapsed, Progressive or Refractory B-Cell Lymphoma." This trial was sponsored and conducted by Genmab, with AbbVie as the collaborator. The information covered all the investigators from the 58 sites that enrolled at least 1 patient in the pivotal cohort from the start of the study on 01 February 2018 to the

database lock on 30 April 2022. Although a total of 3 investigators were identified who had financial payments above $25,000, we agree with the Applicant position, as stated in "Financial Disclosure" Sub-section in Section 8.1.2, that these payments were unlikely to bias study results based on the rationale provided.

Covered Clinical Study (Name and/or Number):* GCT3013-01

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 572		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 3		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 3 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in study: 0 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 6		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

*The table above should be filled by the applicant, and confirmed/edited by the FDA.

19.3. Nonclinical Pharmacology/Toxicology

Data:
N/A

The Applicant's Position:
All nonclinical pharmacology and toxicology data are included in Section 5.

The FDA's Assessment:
The FDA concurs.

19.4. OCP Appendices (Technical documents supporting OCP recommendations)

19.4.1. Epcoritamab Pharmacokinetics

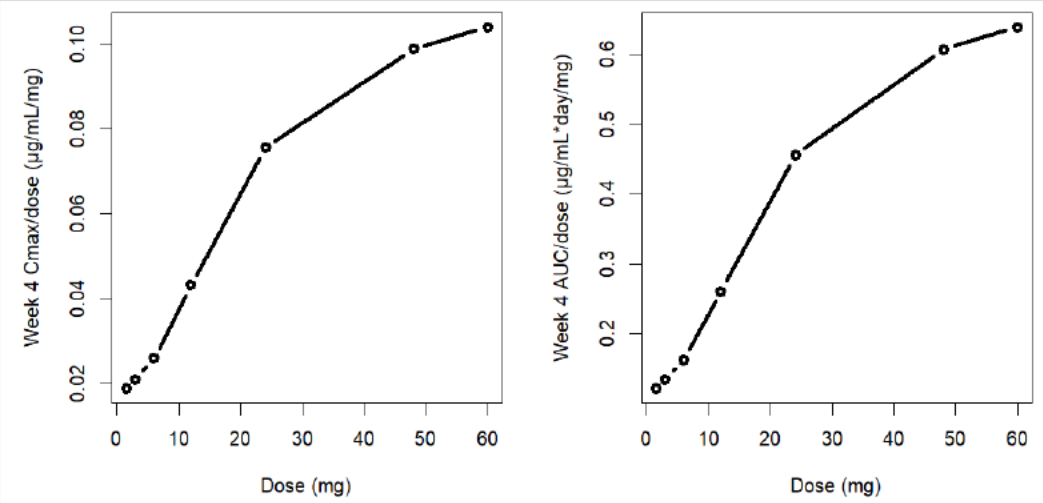
Dose Proportionality
Epcoritamab elimination showed nonlinear characteristics when evaluated using population PK (popPK) analysis (Figure 14). Population predictions of Cmax, dose-normalized Cmax, AUC, dose-normalized AUC at the second full dose (Week 4) (see Table 86). The epcoritamab popPK model is described in detail in Section 19.4.4.

Table 86: Dose Proportionality Assessment Using Final Population Pharmacokinetics Model

Cohort	Full dose (mg)	Cmax (µg/mL)	Cmax/dose (µg/mL/mg)	AUC (µg/mL·day)	AUC/dose (µg/mL·day/mg)
Week 4					
7	3	0.0633	0.0211	0.405	0.135
8	6	0.156	0.0260	0.976	0.163
9	12	0.519	0.0432	3.13	0.261
10	24	1.81	0.0756	10.9	0.456
11	48	4.75	0.0989	29.2	0.608
12	60	6.21	0.104	38.4	0.640
Week 12					
6	1.5	0.0819	0.0546	0.548	0.365
7	3	0.217	0.0724	1.43	0.477
8	6	0.691	0.115	4.43	0.739
9	12	2.00	0.167	12.8	1.07
10	24	4.82	0.201	31.2	1.30
11	48	10.5	0.220	68.6	1.43
12	60	13.4	0.223	87.3	1.46

Source: Table 27 in Applicant's PopPK Report

Figure 14: Relationships Between Predicted Week 4 Exposures and Full Dose

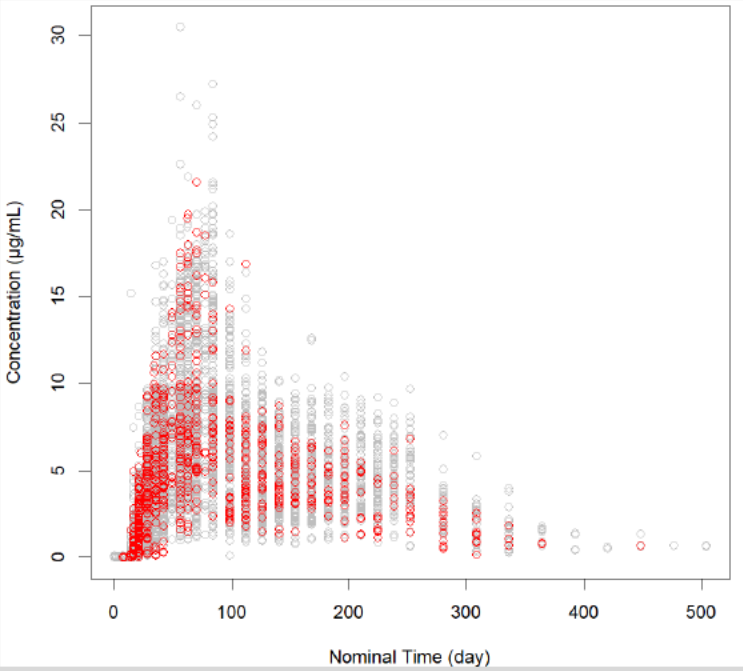


Source: Table 7, Summary of Clinical Pharmacology, Module 2.7.2

Site of Injection

Comparisons of PK data following injections in the abdomen (4790 doses) and thigh (639 doses) indicate that the PK were comparable between these patients (Figure 15).

Figure 15: Scatterplot of Observed Concentration (over Time) Following Injections in the Abdomen (Grey) and Thigh (Red)



The red circles are the observed PK data following an injection in the thigh and the grey circles represent observed PK data following an injection in the abdomen. Observed data are represented for the 48 mg full dose

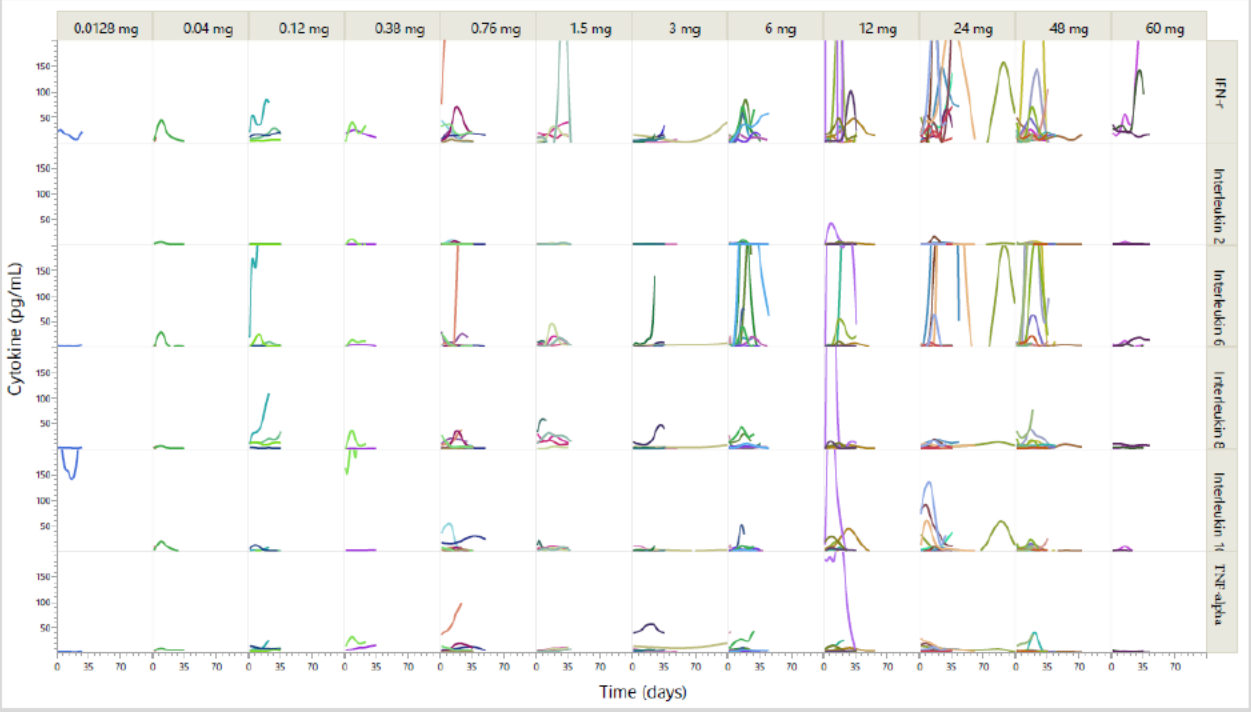
Source: Figure 1, Response of Information Request, SDN 34

19.4.2. Epcoritamab Pharmacodynamics

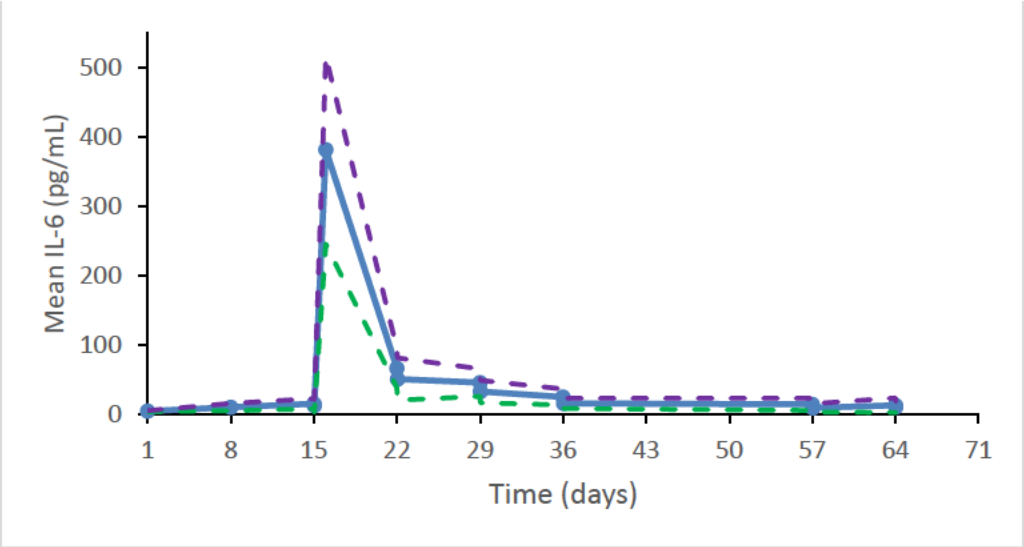
Cytokine Levels
Transient elevation of circulating cytokines was observed at full doses of 0.04 mg and above in the dose escalation portion of GCT3013-01 [Figure 16 (top)].

Cytokine levels were transiently elevated and mostly peaked 24 hours after the first full dose at Cycle 1 Day 15 with levels returning to baseline range prior to next full dose at Cycle 1 Day 22 [Figure 16 (bottom), Table 87]. Median levels of interleukin (IL)-6 in peripheral blood over time in the aNHL cohort are displayed in Figure 17 below. In patients with iNHL and MCL, similar IL-6 release profiles were also observed, with the maximum IL-6 release reported after the first full dose at Cycle 1 Day 15. Similar time course was also observed for interferon (INF)-γ, IFN-α, IL-10, and tumor necrosis factor (TNF)-α (not shown).

Figure 16: Cytokine levels over time by full dose and patients in GCT3013-01 Dose Escalation Part (top), and mean IL-6 levels in peripheral blood over time in patients in aNHL Cohort – GCT3013-01 Expansion Part (Full Analysis Set) (bottom)



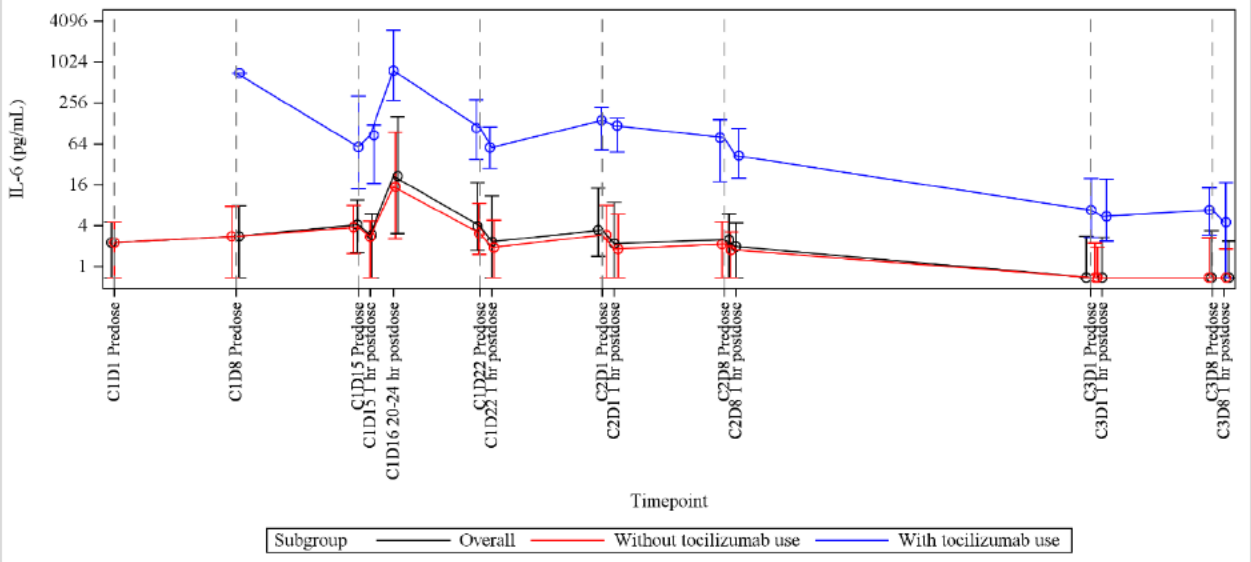
Each line represents a patient. Figure was created from ADLB dataset of GCT3013-01 Escalation phase. IFN-γ represents interferon gamma and TNF-alpha represents tumor necrosis factor.
Source: Reviewer generated.



Blue refers to mean, dashed lines represent lower (green) and upper (purple) 90% confidence intervals.
Source: Reviewer generated.

The patients who received tocilizumab treatment were flagged at all time points after tocilizumab treatment (Figure 17, Table 87).

Figure 17: Median IL-6 levels in peripheral blood over time in in the presence and absence of tocilizumab in patients in aNHL Cohort – GCT3013-01 Expansion Part (Full Analysis Set)



The error bars represent the IQR. Samples collected after first tocilizumab use are categorized as with tocilizumab use.
Source: Figure fda.ir16.q2.anhl, Appendix 1, Response of Information Request, SDN 34

Table 87: Summary of IL-6 by Cycles in patients in aNHL Cohort of GCT3013-01 Expansion Part (Full Analysis Set)

Cycle	Dose (mg)	Timepoint	N	Mean (SD)	Median	(2.5th, 97.5th percentile)	Range
C1D1	0.16	pre-dose	156	31.5 (339.82)	2.3	(0.7, 26.1)	0.7, 4248.0
		pre-dose: Without tocilizumab use	156	31.5 (339.82)	2.3	(0.7, 26.1)	0.7, 4248.0
		pre-dose: With tocilizumab use	0				
C1D8	0.16	pre-dose	1	10.3 (-)	10.3	(10.3, 10.3)	10.3, 10.3
		pre-dose: Without tocilizumab use	1	10.3 (-)	10.3	(10.3, 10.3)	10.3, 10.3
		pre-dose: With tocilizumab use	0				
	0.8	pre-dose	151	31.5 (257.10)	2.8	(0.7, 62.3)	0.7, 3090.0
		pre-dose: Without tocilizumab use	150	27.0 (251.98)	2.7	(0.7, 45.8)	0.7, 3090.0
		pre-dose: With tocilizumab use	1	703.0 (-)	703.0	(703.0, 703.0)	703.0, 703.0
C1D15	48	pre-dose	145	21.5 (85.31)	4.1	(0.7, 280.0)	0.7, 844.0
		pre-dose: Without tocilizumab use	138	12.1 (41.81)	3.8	(0.7, 63.6)	0.7, 395.0
		pre-dose:With tocilizumab use	7	208.3 (303.34)	57.7	(2.3, 844.0)	2.3, 844.0
	48	1 hr post	99	71.3 (542.28)	2.9	(0.7, 126.0)	0.7, 5336.0
		1 hr post: Without tocilizumab use	93	62.9 (552.92)	2.7	(0.7, 51.0)	0.7, 5336.0
		1 hr post: With tocilizumab use	6	201.2 (341.85)	85.2	(7.9, 892.0)	7.9, 892.0
C1D16	48	20-24 post-dose	140	313.5 (950.46)	21.5	(0.7, 3396.0)	0.7,1 5696
		20-24 Without tocilizumab use		155.6 (583.27)	14.9	(0.7, 811.0)	0.7, 5696
		20-24 post-dose: With tocilizumab	14	1734.5 (1992.97)	758.5	(4.4, 5696.0)	4.4, 5696
C1D22	48	pre-dose	142	61.7 (250.75)	3.9	(0.7, 880.0)	0.7, 2342.0
		pre-dose: Without tocilizumab use	122	12.9 (50.24)	3.1	(0.7, 43.7)	0.7, 515.0
		pre-dose: With tocilizumab use	20	359.3 (584.80)	110.0	(17.9, 2342.0)	17.9, 2342.0
	48	1 hr post	100	53.6 (275.39)	2.3	(0.7, 692.0)	0.7, 2542.0
		1 hr post: Without tocilizumab use	84	6.7 (19.64)	1.9	(0.7, 33.0)	0.7, 169.0
		1 hr post: With tocilizumab use	16	299.8 (649.15)	56.5	(10.9, 2542.0)	10.9, 2542.0
C2D1	48	pre-dose	134	72.5 (416.87)	3.5	(0.7, 350.0)	0.7, 4572.0
		pre-dose: Without tocilizumab use	117	47.7 (422.21)	2.9	(0.7, 82.0)	0.7, 4572.0
		pre-dose:	17	242.9 (341.83)	143.7	(12.4, 1123.0)	12.4, 1123.0
	48	1 hr post	127	24.5 (102.52)	2.2	(0.7, 152.0)	0.7, 1085.0
		1 hr post: Without tocilizumab use	113	6.2 (15.73)	1.8	(0.7, 71.1)	0.7, 133.6
		1 hr post: With tocilizumab use	14	172.5 (270.65)	119.5	(10.8, 1085.0)	10.8, 1085.0
C2D8	48	pre-dose	122	43.3 (236.07)	2.5	(0.7, 244.0)	0.7, 2430.0
		pre-dose:Without tocilizumab use	107	30.7 (237.29)	2.2	(0.7, 90.5)	0.7, 2430.0
		pre-dose: With tocilizumab use	15	133.1 (213.29)	78.4	(4.8, 856.0)	4.8, 856.0
	48	1 hr post	118	10.7 (31.09)	2.0	(0.7, 115.0)	0.7, 226.0
		1 hr post: Without tocilizumab use	105	3.4 (5.73)	1.8	(0.7, 20.1)	0.7, 39.4
		1 hr post: With tocilizumab use	13	69.5 (70.18)	43.2	(4.3, 226.0)	4.3, 226.0
C3D1	48	pre-dose	107	19.2 (119.98)	0.7	(0.7, 68.9)	0.7, 1139.0
		pre-dose: Without tocilizumab use	94	14.3 (117.3)	0.7	(0.7, 12.8)	0.7, 1139.0
		pre-dose: With tocilizumab use	13	54 (137.89)	6.7	(0.7, 507.0)	0.7, 507.0
	48	1 hr post	100	16 (115.27)	0.7	(0.7, 53.9)	0.7, 1143.0
		1 hr post: Without tocilizumab use	90	14.7 (120.33)	0.7	(0.7, 8.7)	0.7, 1143.0
		1 hr post: With tocilizumab use		27.4 (53.27)	5.5	(0.7, 172.0)	0.7, 172.0

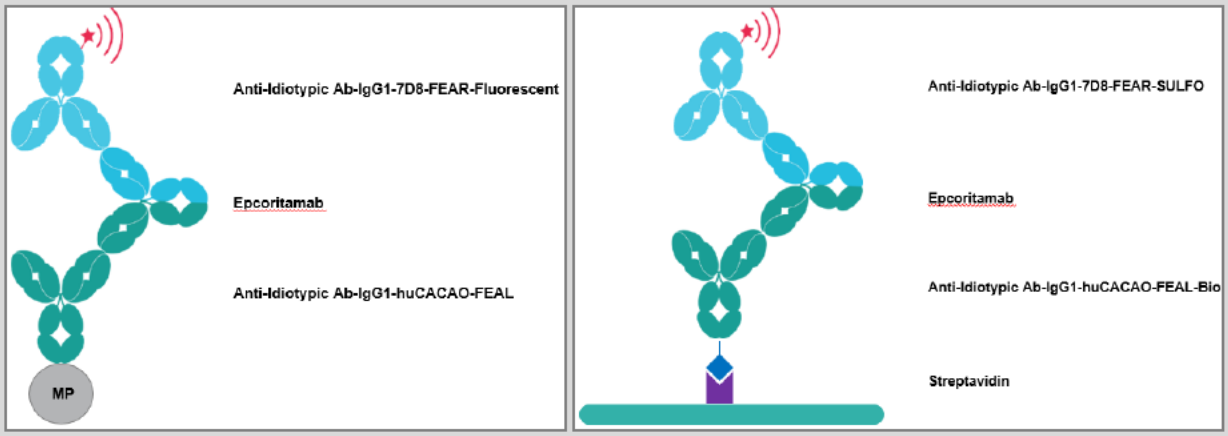
Source: Table fda.ir16.q2.anhl, Appendix 1, Response of Information Request, SDN 34

Circulating B Cell Count
Circulating B cells decreased to undetectable levels (< 10 cells/microliter) after administration of the of epcoritamab in patients who had detectable B cells at treatment initiation by Cycle 1 Day 15 (after the first full dose of 48 mg) and the depletion was sustained while patients remained on treatment.

19.4.3. Bioanalytical Method

Two bioanalytical assays, namely, SMCIA-139 and ECLIA-139, were used to quantify epcoritamab (free; not bound to CD3 and/or CD20) in human plasma for PK evaluation. The SMCIA-139 method (quantitation range: 60-500 pg/mL) is a fluorescent sandwich immunoassay technique while ECLIA-139 method (quantitation range: 10-1000 ng/mL) is an electrochemiluminescence sandwich immunoassay (see Figure 18).

Figure 18: Method for Quantification of Epcoritamab Using SMCIA-139 Assay (left) and ECLIA assay (right)



Abbreviations: Ab = antibody; IgG1 = immunoglobulin G1; MP = microparticle
Source: Figures 1 and 2, Module 2.7.1

Both methods were validated. All PK samples for the GCT3013-01 Expansion phase and the GCT3013-04 trials, and 57% of all PK samples from the Dose Escalation phase of GCT3013-01 were analyzed using the ECLIA-139 assay. The SMCIA-139 bioanalytical method was used only in the Dose Escalation Part of GCT3013-01. A cross-validation between SMCIA-139 and ECLIA-139 assays was performed to determine the comparability of the methods. The cross-validation results indicated only 43% of the samples were within ≤30% of original values. Consequently, only measured PK data generated using the ECLIA-139 method were included from the escalation phase of GCT3013-01. Therefore, this review mainly focuses on ECLIA-139 assay. The primary PPK analysis (Section **Error! Reference source not found.**) only included PK s amples measured using the ECLIA-139 assay. Per Genmab, a sensitivity analysis confirmed that

not including the SMCIA-139 PK data had little or no impact on the final epcoritamab PPK model.

A third assay, referred to as the ECLIA-101 assay, was developed and validated during the epcoritamab development program, but the data were not used in this submission.

19.4.3.1. Validation

In the ECLIA-139 assay, epcoritamab is captured with a biotinylated antibody, directed against the idiotype of IgG1-huCACAO-FEAL of epcoritamab, which is bound to a streptavidin-coated microtiter ECL plate. A SULFO-TAG conjugated detection antibody directed against the IgG1-7D8-FEAR arm of epcoritamab binds to the captured epcoritamab molecule [Figure 18 (right)]. After incubation, electrochemical stimulation is initiated. Elicited SULFO-TAG label emits light at 620 nm, which is measured with an MSD-ECL plate reader. The amount of emitted light is an indirect readout for the concentration of epcoritamab in the sample.

Table 88: Method validation parameters for ECLIA-139 assay

Validation Parameters	ECLIA-139 (GNM20420-20420X-B)
Analyte	Epcoritamab
Detection	Electrochemiluminescence sandwich immunoassay [see Figure 18 (left) and description above]
Anticoagulant	K_2EDTA plasma
Range	10.0 to 1000 ng/mL, with anchor points at 1.00 ng/mL, 7.50 ng/mL and 1500 ng/mL
Minimum Required Dilution	1:20
Calibrators Concentrations	10, 25, 100, 250, 500, 750, 900, 1000 ng/mL
Regression model and weighting	4-parameter logistic with $1/Y^2$ weighting factor
Anchor points	1, 7.5, 1500 ng/mL
Quality Controls	10 (LLOQ), 30, 150, 750, and 1000 (ULOQ) ng/mL
Intra/Inter-assay Precision at LLOQ (%CV)	<10% / <9.6%
Intra/Inter-assay Accuracy at LLOQ	-4.6 to 5.7% / 5.5%
Total Error	≤19.4%
Inter/Intra-assay Precision (%CV)	<11% / <8.1%
Inter/Intra-assay Accuracy (% accuracy)	-12.5 to 14.1% / -2.4 to 3.5%
Selectivity (accuracy %)	Healthy subjects: 90% of 10 blank lots had no interference. 90% of 10 lots spiked at the LLOQ were <20% of the nominal concentration. Disease State: 100% of 30 blank lots had no interference. 70% of 30 lots spiked at the LLOQ were <25% of nominal concentration. Hemolysis: <LLOQ in blank lot 2 of 3 replicates at the LLOQ were <25% of nominal concentration Lipemic: All replicates at the LLOQ were <25% of nominal concentration

Validation Parameters	ECLIA-139 (GNM20420-20420X-B)
	With rituximab: All 3 lots spiked at the LLOQ and at 750 ng/mL* were 20% of nominal concentration (*one lot at 750 ng/mL was 22% of nominal)
Dilution Linearity (% accuracy)	Serial 2-fold dilutions from 7500 ng/mL in pooled plasma analyzed in 3 runs: 14.6 to 938 ng/mL (512x to 8x): up to -15.9% in 3 lots, except in 2 of 3 lots at 14.6 ng/mL bias was > -20% (-20.1%, -26.2%)
10-fold Dilution [%Bias (%CV)]:	300 ng/mL: 4.5% (10.6%) 7500 ng/mL: -1.5% (3.6%)
Stock stability [%Bias (%CV)]	316 days at RT: 1% (5%)
Bench-top stability [%Accuracy (%CV)]	24 hours at RT: <10% (<10%)
Extract stability	163 hours at 2°C to 8°C
Long-term Stability [%Accuracy (%CV)]	603 days at -70°C at 750 and 7500 ng/mL†: <20% (<5%) 448 days at -70°C at 30, 750, and 7500 ng/mL: <20% (<5%)
Freeze-Thaw Stability [%Accuracy (%CV)]	5 cycles at -70°C: <7% (<9%) 5 cycles at -20°C: <2% (<2%)
Assay used in Clinical Studies	GCT3013-01 (57% of samples for Escalation phase and all samples for Expansion phase) and GCT3013-04

LLOQ= lower limit of quantitation, ULOQ=upper limit of quantitation
Accuracy and Precision acceptance [Accuracy (CV)]: ≤20% (≤20%) except ≤25% (≤25%) at LLOQ and ULOQ,
Total error: ≤30% (≤40% at LLOQ & ULOQ)
Stability and dilution linearity acceptance: [Accuracy (CV)]: <20% (<20%)
Selectivity acceptance: 2 of 3 determinations ≤25% at LLOQ (≤20% at HQC, if included)
† Report GNM20420-20420X-B Am 01

19.4.3.2. Bioanalytical Report

The validated ECLIA-139 method was used for analysis of study samples in GCT3013-01 and -04 trials (Table 89). In Studies GCT3013-01 and -04, the precision was ≤10% and accuracy was ≤10% (Table 90 and Table 91). Majority (70-80%) of the analytical runs in the studies were successful. The incurred sample reanalysis (ISR) performed in the studies were within the acceptable limits, with ≥70-80% of samples within relative difference of ≤30%.

The study sample concentrations reported were analyzed within the validated storage and handling conditions. The maximum storage period at -70°C between blood sampling and sample analysis was 819 days in Study GCT3013-01 were beyond the validated frozen storage period. Nonetheless, results from 393 samples of the Escalation phase and 3 samples of the Expansion phase of GCT3013-01 were not reported as they were analyzed outside the validated storage. All patient samples in Study GCT3013-04 were analyzed within the validated frozen storage stability.

Table 89: Summary of method parameters of ECLIA-139 assay used in GCT3013-01 and GCT3013-04

Parameters	GCT3013-01 and GCT3013-004 (Report GNM012EL-170123-C, Report GNM20899-20899X-A)
Analyte	Epcoritamab
Method	ECLIA-139
Anticoagulant	K_2EDTA plasma
Range	10.0 to 1000 ng/mL, with anchor points at 1.00 ng/mL, 7.50 ng/mL and 1500 ng/mL
Calibrators Concentrations	10, 25, 100, 250, 500, 750, 900, 1000 ng/mL
Anchor points	1, 7.5, 1500 ng/mL
Minimum Required Dilution	1:20
Regression model and weighting	4-parameter logistic with $1/Y^2$ weighting factor
Quality Controls	30, 150, and 750 ng/mL, and diluted QCs 7500 ng/mL at 20x and 40x

Table 90: Summary of performance of ECLIA-139 assay in GCT3013-01

Parameters	GCT3013-01 (Report GNM012EL-170123-C)
Inter-assay Precision (%CV)	<10%
Inter-assay Accuracy	1.1% to 1.9%
Diluted QCs [%Accuracy (%CV)]	-1% to 1% (<11%)
Analytical run pass rate	70% Mainly rejected for not meeting QC acceptance criteria
Reanalyses	9% of study samples were reanalyzed mainly as original values were >ULOQ.
Parallelism	10 patient samples at Cmax range diluted serially to 5 concentrations. For each patient sample, CV of the back-calculated concentrations were <30%
Incurred Sample Reanalysis (ISR)	Of the 501 samples reanalyzed for ISR, 79% were within 30% of original values
Sample storage	The maximum storage period at -70 °C between blood sampling and sample analysis was 819 days. Therefore, 393 samples in the Escalation phase and 3 samples in the Expansion phase that were analyzed outside the validated storage stability period and were not reported.[#]

[#] from Report GNM012EL-170123-C, Amendment 1

Table 91: Summary of performance of ECLIA-139 assay in GCT3013-04

Parameters	GCT3013-04 (Report GNM20899-20899X-A)
Inter-assay Precision (%CV)	<9%
Inter-assay Accuracy	-1.2% to 1.7%
Diluted QCs [%Accuracy (%CV)]	1.1% (<9%)
Analytical run pass rate	80% Mainly rejected for not meeting QC acceptance criteria

Parameters	GCT3013-04 (Report GNM20899-20899X-A)
Reanalyses	9% of study samples were reanalyzed mainly as original values were >ULOQ. 2% of study samples were intended to be reanalyzed but were not due to site change.
Parallelism	10 patient samples at Cmax range diluted serially to 5 concentrations. For each patient sample, CV of the back-calculated concentrations were <30%
Incurred Sample Reanalysis (ISR)	Of the 124 samples reanalyzed, 72% were within 30% of original values
Sample storage	The maximum storage period at -70 °C between blood sampling and sample analysis was 311 days.

19.4.4. Population PK Analysis

19.4.4.1. Executive Summary

The FDA's Assessment:
The PPK model generally adequately characterizes epcoritamab PK, and the model-predicted exposure metrics of AUC and C_{trough} are adequate for use in E-R analysis.

No dosage adjustments are recommended according to weight, age, sex, Asian or White racial category, mild to moderate renal impairment, or mild hepatic impairment. Lower body weight was associated with higher exposure, but the exposure difference according to body weight is not expected to have a significant impact on clinical outcomes. The effects of severe renal impairment, end-stage renal disease, and moderate to severe hepatic impairment on the PK of epcoritamab are unknown.

19.4.4.2. PPK Assessment Summary

The Applicant's Position:

General Information	
Objectives of PPK Analysis	• To develop a population PK model of epcoritamab following SC administration in the patient populations of GCT3013-01 and GCT3013-04. Specifically: • To obtain estimates of typical PK parameters and of inter- and intra-individual variability of the PK parameters; • To evaluate effects of ADA on epcoritamab PK; • To evaluate the effects of subjects' demographic characteristics (weight, age, sex, race) and other covariates (eg, laboratory tests, baseline disease status) on epcoritamab PK;

		• To assess the epcoritamab exposure in special populations (eg, subjects with renal and hepatic impairment, and elderly subjects); • To derive predicted individual exposures (eg, AUC, Cmin, or/and Cmax) of epcoritamab for the exposure-safety and exposure-efficacy analyses.
Studies Included		GCT3013-01 and GCT3013-04
Dose(s) Included		Priming doses of epcoritamab tested include 0.004, 0.0128, 0.04, 0.08, 0.12, and 0.16 mg. Intermediate doses of epcoritamab tested include 0.25, 0.5, 0.8, and 1.6 mg. Full doses of epcoritamab tested include 0.0128, 0.04, 0.12, 0.38, 0.76, 1.5, 3, 6, 12, 24, 48, and 60 mg
Population Included		R/R LBCL, iNHL, and MCL
Population Characteristics	General	Age median (range) 67 [20-89] years Weight median (range) 70 [39-144] kg 195 (59.6%) male / 132 (40.4%) female 185 (56.6%) White; 99 (30.3%) Asian; Native American 1 (0.3%); 42 (12.8%) other
	Organ Impairment	Hepatic (Child-Pugh, NCI, etc): 270 (82.6%) normal, 53 (16.2%) mild impairment, 1 (0.3%) moderate impairment Renal (CrCL, etc): 110 (33.6%) normal, 147 (45%) mild impairment, 68 (20.8%) moderate impairment
	Pediatrics (if any)	N/A
No. of Patients, PK Samples, and BLQ		327 patients; 6819 quantifiable PK samples and 953 BLQ
Sampling Schedule	Rich Sampling	GCT3013-01 escalation: • 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 cycle 3-6 • At predose during 1st dose in cycle 7 and onward GCT3013-04 escalation: • Predose after 1st dose in cycle 1 • At predose, 1 hour (after dose), 2, 3 and 4 days during 2nd and 3rd dose in cycle 1 • At predose, 1, 6 hours (after dose), 2 and 5 days after 4th dose in cycle 1 • At predose after 1st, 2nd, 3rd, and 4th dose in cycle 2-3 • At predose after 1st and 3rd dose in cycle 4-9 • At predose after 1st dose in cycle 10 and onward
	In ITT Population	GCT3013-01 expansion: • 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 cycle 2-3

		• At predose and 1 hour (after dose) during 1st and 3rd dose in cycle 4-9 • At predose and 1 hour (after dose) during 1st dose in cycle 10 and onward GCT3013-04 expansion: • Predose after 1st dose in cycle 1 • At predose, and 1 hour (after dose) 2nd, 3rd, and 4th dose in cycle 1 • At predose after 1st, 2nd, 3rd, and 4th dose in cycle 2-3 • At predose after 1st and 3rd dose in cycle 4-9 • At predose after 1st dose in cycle 10 and onward
Covariates Evaluated	Static	age, weight, body surface area, body mass index, albumin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, bilirubin, lactate dehydrogenase, serum creatinine, SPD, natural log of SUMPPD, creatinine clearance, BSA-normalized creatinine clearance, time from the last CD20 therapy, T-cell counts, B-cell counts, sex, race, region, renal impairment, hepatic impairment, ECOG, age group, weight group, albumin group, Ann Arbor stage, lymphoma subtype, prior lines of therapy, prior CAR-T therapy, prior AST therapy, prior CD19 therapy, refractory to prior anti-lymphoma therapy, refractory to prior anti-CD20 therapy, relapsed after prior anti-CD20 therapy, time from last anti-CD20 therapy, ADA status and titer
	Time-varying	None

Final Model	**Summary**	**Acceptability [FDA's comments]**
Software and Version	NONMEM software, Version 7.5.0 (ICON Development Solutions)	The final PPK model adequately characterizes epcoritamab PK.
Model Structure	QSS approximation of the two-compartment epcoritamab TMDD model with the first order SC absorption	
Model Parameter Estimates	Table 94	
Uncertainty and Variability (RSE, IIV, Shrinkage, Bootstrap)	All structural model parameters were estimated precisely; RSE did not exceed 10.9%. The covariate effects parameters were also estimated precisely; RSE did not exceed 16.6% except for the effect of age on ka (RSE of 33.0%). All variance parameters were also estimated precisely (RSEs 9.25-20.3%). Shrinkage of the inter-individual random effects was low to moderate, below 34.2% except for the kint parameter (43.1%). Shrinkage of the residual error was low (4.1%). The IIV was low for epcoritamab main PK parameters CL/F (CV=25.7%) and VC/F (CV=31.2%), but was high for all other parameters (CV of 55 to 138%). The intra-individual (residual) variability was low (CV=18.9%). The IIV on the magnitude of the	

Final Model	Summary	Acceptability [FDA's comments]
	intra-individual (residual) error was estimated as 21.2%.	
BLQ for Parameter Accuracy	To evaluate the impact of BQL measurements on the PK model, the final model (Model 154) was re-estimated after adding the BQL measurements to the data and using a likelihood approach to incorporate the BQL data into the model (Model 154bql [popPK report Table 24]). The parameter estimates of this BQL model were similar to those of the final model (Model 154) (Table 94). Moreover, the individual and population predictions of these models were nearly identical. Therefore, this sensitivity analysis confirmed that exclusion of BQL data had little impact on the population PK model. BQL data had minimal impact on the final model.	The majority of BQL samples were taken following a last dose of ≤0.8 mg (i.e., step-up doses) (836 out of 953 BQL samples [88%]). Because the purposes of the model relate to PK and exposure with the full dose (48 mg), exclusion of BQL samples from the PPK model input is acceptable.
GOF, VPC	GOF plots (Figure 19) VPC plots: overall and by trial (Figure 20) and by lymphoma subtypes (Figure 21) The final model adequately described the PK data.	GOF plots on a linear scale are presented in **Figure 22**. The PPK model adequately characterizes concentrations approximately 0.1 ug/mL up to 15 ug/mL. The model under-estimates epcoritamab concentrations of 15 ug/mL and above, and thus model-predicted C_{max} is likely less accurate than model-predicted AUC and C_{trough}.
Significant Covariates and Clinical Relevance	Baseline body weight had a significant effect on epcoritamab PK. Similar impact of body weight on PK have been observed for other therapeutic antibodies (Dirks and Meibohm, 2010). Exposure decreased with increasing weight across baseline weight categories: <65 kg (n=116 subjects), 65 to <85 kg (n=136 subjects), and ≥85 kg (n=75 subjects). Since efficacy and safety were generally consistent across body weight categories, the differences in exposure among different weight groups were not considered clinically meaningful. Age was a statistically significant covariate on the absorption rate constant but did not influence other PK parameters (M2.7.2 Section 3.2.2.3). Comparison of epcoritamab exposure among subjects <65 years, 65 to <75 years,	No dosage adjustments are recommended according to weight, age, sex, race, mild to moderate renal impairment, or mild hepatic impairment.

Final Model	Summary	Acceptability [FDA's comments]
	and ≥75 years did not show any meaningful differences or age-related trends. No clinically meaningful differences in efficacy or safety in subgroups by age were observed.	
Analysis Based on Simulation (optional)	N/A	

Labeling Language	Description	Acceptability [FDA's comments]
12.3 PK	(b) (4)	The proposed labeling is acceptable upon the Applicant and FDA reaching agreements to the FDA-recommended revisions to the labeling, which included updates regarding formatting and clear reporting of descriptive statistics. Absorption The median (range) T_{max} of epcoritamab after the first full dose and end of the weekly dosing regimen (end of Cycle 3) treatment doses were 4.0 (0.3 to 7) days and 2.3 (0.3 to 3.2) days, respectively. Distribution The geometric mean (% CV) apparent total volume of distribution is 25.6 L (81.8%). Elimination The geometric mean (% CV) half-life of full dose epcoritamab-bysp (48 mg) ranged from 22 (57.8%) to 25 days (73.5%) after Cycle 3, after Cycle 9, and after steady state of Q4W dosing. Epcoritamab-bysp is cleared by parallel linear and nonlinear saturable target mediated clearances. The geometric mean (CV%) apparent total clearance is 3.34 L/day (102%) at the first full treatment dose and 0.53 L/day (39.7%) at the 11th full dose. *Metabolism*

Labeling Language	Description	Acceptability [FDA's comments]
	(b) (4)	Epcoritamab-bysp is expected to be metabolized into small peptides by catabolic pathways. Specific Populations No clinically significant differences in the PK of epcoritamab-bysp were observed based on age (20 to 89 years), sex, race (White or Asian), mild to moderate renal impairment (CLcr ≥ 30mL/min to <90 mL/min), and mild hepatic impairment (total bilirubin ≤ ULN and AST > ULN, or total bilirubin 1 to 1.5 times ULN and any AST) after accounting for differences in bodyweight. The effects of severe renal impairment (CLcr 15-30 mL/min), end-stage renal disease (CLcr <15mL/min), or moderate to severe hepatic impairment (total bilirubin > 1.5 times ULN and any AST) on the PK of epcoritamab-bysp are unknown. *Body Weight* In patients with relapsed or refractory LBCL who received the recommended dosage of EPKINLY, Cycle 1 geometric mean average concentration was 19% lower in the higher body weight (BW) group (85 kg and above) and 29% higher in the lower BW group (less than 65 kg) compared to patients with BW of 65 to less than 85 kg.

Table 92: Applicant - Summary of Continuous Covariates: Median [Range]

Covariate Description	GCT3013-01 Escalation	GCT3013-01 Expansion	GCT3013-04	Total
Number of patients	35	232	60	327
Age (years)	69 [24-84]	67 [20-86]	66 [42-89]	67 [20-89]
Weight (kg)	74 [52-144]	74 [39-129]	55 [39.1-96.1]	70 [39-144]
Body surface Area (m^2)	1.88 [1.56-2.68]	1.84 [1.29-2.46]	1.55 [1.29-2.06]	1.82 [1.29-2.68]

Covariate Description	GCT3013-01 Escalation	GCT3013-01 Expansion	GCT3013-04	Total
Body mass Index(kg/m^2)	25.9 [17.9-41.4]	25.2 [15.7-44]	22.3 [17-33.6]	24.4 [15.7-44]
Albumin (g/L)	37 [30-48]	39 [22-50]	40 [26-49]	39 [22-50]
Alkaline phosphatase (u/L)	85 [54-165]	94 [32-500]	97 [49-447]	93 [32-500]
Alanine aminotransferase (u/L)	24 [6-137]	19 [2.5-150]	16 [4-49]	19 [2.5-150]
Aspartate aminotransferase (u/L)	22 [9-54]	24 [9-101]	21 [12-52]	23 [9-101]
Bilirubin (µmol/L)	7 [2-19]	8 [1-51]	10.3 [5.13-22.2]	8.55 [1-51]
Lactate dehydrogenase (u/L)	229 [123-1540]	275 [117-2030]	246 [152-2060]	267 [117-2060]
Serum creatinine (µmol/L)	0.915 [0.599-1.95]	0.833 [0.25-1.95]	0.754 [0.489-1.84]	0.825 [0.25-1.95]
Sum of the products of perpendicular diameters per investigator (cm^2)	36.8 [3.8-206]	32.4 [2.01-326]	19.9 [1.96-178]	30.4 [1.96-326]
Natural log of SUMPPD (cm^2)	3.61 [1.34-5.33]	3.48 [0.696-5.79]	2.99 [0.672-5.18]	3.42 [0.672-5.79]
Creatinine clearance (mL/min)	77 [45-134]	81.7 [31-308]	70.7 [35.1-126]	78 [31-308]
BSA-normalized creatinine clearance (mL/min/1.73m^2)	70.6 [39.5-111]	79.1 [33-268]	72.1 [46.9-119]	76.3 [33-268]
Time from the last CD20 therapy (month)	7.49 [2.27-178]	6.24 [0.657-153]	5.72 [0.0986-111]	6.21 [0.0986-178]
T-cell counts (cell/µL)	560 [33-2190]	630 [19-2700]	-	613 [19-2700]
B-cell counts (cell/µL)	0 [0-1780]	0 [0-1800]	-	0 [0-1800]

Abbreviations: BSA = body surface area; CD = cluster of differentiation; SUMPPD = baseline tumor size, sum of products of perpendicular diameters.
Source: ContCovMean.csv (PrepareReportPlots_Final.R)

Table 93: Applicant - Summary of Categorical Covariates

Covariate	Level	GCT3013-01 Escalation	GCT3013-01 Expansion	GCT3013-04	Total
N (%)		35 (10.7%)	232 (70.9%)	60 (18.3%)	327 (100%)
Sex (SEX)	Male	22 (62.9%)	142 (61.2%)	31 (51.7%)	195 (59.6%)
	Female	13 (37.1%)	90 (38.8%)	29 (48.3%)	132 (40.4%)
Race (RACE)	White	35 (100%)	150 (64.7%)	-	185 (56.6%)
	Asian	-	39 (16.8%)	60 (100%)	99 (30.3%)
	Native A/Am	-	1 (0.4%)	-	1 (0.3%)
	Other	-	42 (18.1%)	-	42 (12.8%)
Region	Asia	-	36 (15.5%)	60 (100%)	96 (29.4%)
	Australia	-	31 (13.4%)	-	31 (9.5%)
	Europe	35 (100%)	135 (58.2%)	-	170 (52%)
	N. America	-	30 (12.9%)	-	30 (9.2%)
Renal impairment (BRENF)	Missing	-	2 (0.9%)	-	2 (0.6%)
	Normal	12 (34.3%)	89 (38.4%)	9 (15%)	110 (33.6%)
	Mild	16 (45.7%)	100 (43.1%)	31 (51.7%)	147 (45%)
	Moderate	7 (20%)	41 (17.7%)	20 (33.3%)	68 (20.8%)
Hepatic impairment (BHEPF)	Missing	-	3 (1.3%)	-	3 (0.9%)
	Normal	33 (94.3%)	184 (79.3%)	53 (88.3%)	270 (82.6%)
	Mild	2 (5.7%)	44 (19%)	7 (11.7%)	53 (16.2%)

Covariate	Level	GCT3013-01 Escalation	GCT3013-01 Expansion	GCT3013-04	Total
	Moderate	-	1 (0.4%)	-	1 (0.3%)
ECOG	0	19 (54.3%)	112 (48.3%)	40 (66.7%)	171 (52.3%)
	1	12 (34.3%)	113 (48.7%)	18 (30%)	143 (43.7%)
	2	3 (8.6%)	7 (3%)	2 (3.3%)	12 (3.7%)
	3	1 (2.9%)	-	-	1 (0.3%)
Age group	<65 years	10 (28.6%)	102 (44%)	21 (35%)	133 (40.7%)
	≥65, <75 yrs	13 (37.1%)	83 (35.8%)	31 (51.7%)	127 (38.8%)
	≥75 years	12 (34.3%)	47 (20.3%)	8 (13.3%)	67 (20.5%)
Weight group	<65	8 (22.9%)	65 (28%)	43 (71.7%)	116 (35.5%)
	≥65, <85	14 (40%)	107 (46.1%)	15 (25%)	136 (41.6%)
	≥85	13 (37.1%)	60 (25.9%)	2 (3.3%)	75 (22.9%)
Albumin group	Missing	-	2 (0.9%)	-	2 (0.6%)
	<35	8 (22.9%)	48 (20.7%)	9 (15%)	65 (19.9%)
	≥35	27 (77.1%)	182 (78.4%)	51 (85%)	260 (79.5%)
Ann Arbor Stage	1	2 (5.7%)	9 (3.9%)	2 (3.3%)	13 (4%)
	2	5 (14.3%)	37 (15.9%)	10 (16.7%)	52 (15.9%)
	3	6 (17.1%)	38 (16.4%)	19 (31.7%)	63 (19.3%)
	4	22 (62.9%)	148 (63.8%)	29 (48.3%)	199 (60.9%)
Lymphoma subtypes	LBCL	25 (71.4%)	145 (62.5%)	42 (70%)	212 (64.8%)
	iNHL	8 (22.9%)	71 (30.6%)	18 (30%)	97 (29.7%)
	MCL	2 (5.7%)	16 (6.9%)	-	18 (5.5%)
Prior lines of therapy	≤2	15 (42.9%)	64 (27.6%)	24 (40%)	103 (31.5%)
	3	7 (20%)	77 (33.2%)	13 (21.7%)	97 (29.7%)
	≥4	13 (37.1%)	91 (39.2%)	23 (38.3%)	127 (38.8%)
Prior CAR-T therapy	No	30 (85.7%)	165 (71.1%)	58 (96.7%)	253 (77.4%)
	Yes	5 (14.3%)	67 (28.9%)	2 (3.3%)	74 (22.6%)
Prior AST therapy	No	29 (82.9%)	188 (81%)	49 (81.7%)	266 (81.3%)
	Yes	6 (17.1%)	44 (19%)	11 (18.3%)	61 (18.7%)
Prior CD19 therapy	No	34 (97.1%)	224 (96.6%)	60 (100%)	318 (97.2%)
	Yes	1 (2.9%)	8 (3.4%)	-	9 (2.8%)
Refractory to prior anti-lymphoma therapy	No	16 (45.7%)	108 (46.6%)	30 (50%)	154 (47.1%)
	Yes	19 (54.3%)	124 (53.4%)	30 (50%)	173 (52.9%)
Refractory to prior anti-CD20 therapy	No	28 (80%)	133 (57.3%)	41 (68.3%)	202 (61.8%)
	Yes	7 (20%)	99 (42.7%)	19 (31.7%)	125 (38.2%)
Relapsed after prior anti-CD20 therapy	No	28 (80%)	133 (57.3%)	41 (68.3%)	202 (61.8%)
	Yes	7 (20%)	99 (42.7%)	19 (31.7%)	125 (38.2%)
Time from last anti-CD20 therapy	<median	16 (45.7%)	115 (49.6%)	33 (55%)	164 (50.2%)
	≥median	19 (54.3%)	117 (50.4%)	27 (45%)	163 (49.8%)
ADA status and titer[a]	Negative	32 (91.4%)	224 (96.6%)	57 (95%)	313 (95.7%)
	Positive, <1	2 (5.7%)	7 (3%)	1 (1.7%)	10 (3.1%)
	Positive, ≥1	1 (2.9%)	1 (0.4%)	2 (3.3%)	4 (1.2%)

Abbreviations: ADA = anti-drug antibody; AST = aspartate aminotransferase; BHEPF = baseline hepatic function; BRENF = baseline renal function; CAR-T = chimeric antigen receptor T-cell; CD = cluster of differentiation; ECOG = Eastern Cooperative Oncology Group; iNHL = indolent B-cell non-Hodgkin lymphoma; LBCL = large B-cell lymphoma; MCL = mantle cell lymphoma.

[a.] Titer based on maximum of 3 (≤1:640 taking into account all sample dilutions; ie, titer 3 corresponds with the third step in the 2-fold serial dilution series, which is 8, multiplied by the minimal required dilution of the method of 1:80, resulting in a total dilution of 1:640).

Source file: CatCov.csv (PrepareReportPlots_Final.R)

Table 94: Applicant – Parameter Estimates of Final Model 154

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

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

Abbreviations: 95% CI = 95% confidence interval; CV = coefficient of variation; NONMEM = Nonlinear Mixed-Effect Modeling software; RSE% = relative standard error = 100·abs(SE/PE); SE = standard error.

Source: 154ParEst.csv (DiagnosticPlots.R)

Table 95: Applicant – Summary of Individual Model Parameters

PK parameters	GCT3013-01 (ESC+EXP)				GCT3013-04 (ESC+EXP)	
	R/R DLBCL (N=159)		R/R LBCL (N=170)		R/R LBCL (N=42)	
	Mean (SD)	Geomean (CV)	Mean (SD)	Geomean (CV)	Mean (SD)	Geomean (CV)
CL/F (L/day)	0.458 (0.123)	0.441 (0.281)	0.457 (0.122)	0.441 (0.278)	0.375 (0.0871)	0.365 (0.232)

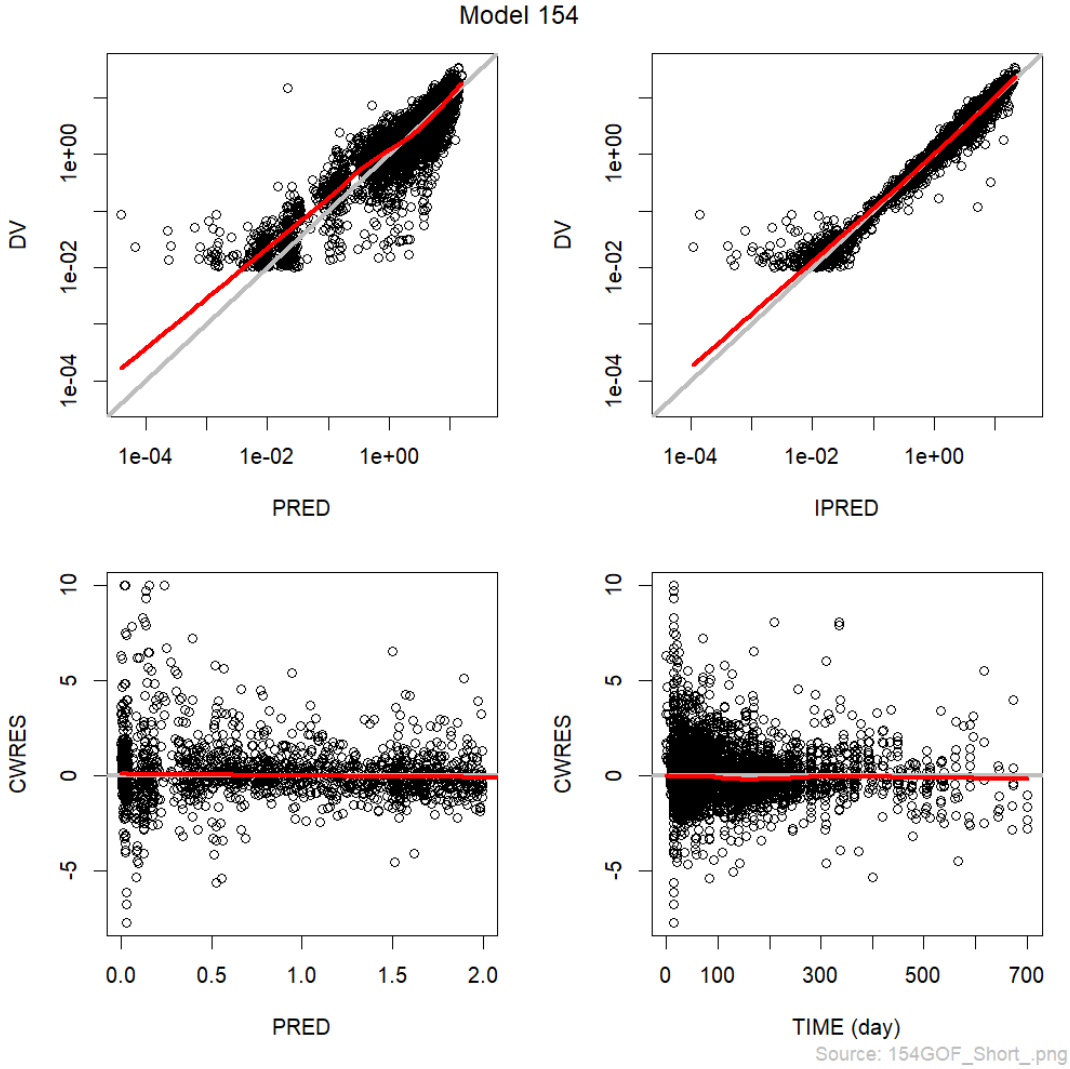
Q/F (L/day)	0.622 (0.483)	0.5 (0.725)	0.624 (0.483)	0.501 (0.725)	0.482 (0.224)	0.434 (0.506)
V_C/F (L)	8.57 (2.25)	8.27 (0.278)	8.56 (2.24)	8.27 (0.275)	7.42 (2.1)	7.17 (0.263)
V_P/F (L)	25.5 (27.3)	14.8 (1.55)	25.1 (28.3)	14.4 (1.55)	18.3 (34.1)	8.34 (1.85)
$V_{SS}/F=(V_C+V_P)/F$ (L)	34 (27.5)	26.1 (0.815)	33.6 (28.5)	25.6 (0.818)	25.8 (34.5)	18.1 (0.829)
k_a (1/day)	0.712 (1.13)	0.595 (0.463)	0.731 (1.07)	0.615 (0.473)	0.747 (0.764)	0.621 (0.55)
BASE (µg/mL)	2.16 (0.826)	2.02 (0.384)	2.19 (0.851)	2.04 (0.393)	2.19 (1.05)	2.01 (0.41)
K_{SS} (µg/mL)	0.243 (0.167)	0.209 (0.572)	0.245 (0.167)	0.21 (0.575)	0.286 (0.271)	0.22 (0.809)
k_{int} (1/day)	0.0359 (0.0236)	0.0319 (0.465)	0.0357 (0.0225)	0.0319 (0.45)	0.0342 (0.0204)	0.0308 (0.428)
$t_{1/2,ka}$ (day)	1.26 (0.434)	1.17 (0.463)	1.22 (0.44)	1.13 (0.473)	1.24 (0.495)	1.12 (0.55)

Abbreviations: BASE = baseline total target concentration; CL/F = apparent clearance; CV = coefficient of variation; k_a = absorption rate constant; DLBCL = diffuse large B-cell lymphoma; ESC = escalation; EXP = expansion; k_a = absorption rate constant; k_{int} = elimination rate constant of the drug-target complex; Kss = QSS constant; LBCL = large B-cell lymphoma; N = number of subjects; PK = pharmacokinetics; Q/F = apparent inter-compartmental clearance; QSS = quasi-steady-state; R/R = relapsed or refractory; SD = standard deviation; $t_{1/2,ka}$ = half-life of absorption rate; V_c/F = apparent volume of distribution in the central compartment; V_p/F = apparent volume of distribution in the peripheral compartment; V_{ss}/F = apparent volume of steady-state.

Individual PK parameters of 338 subjects from the model development data set were used to compute statistics stratified by trial and lymphoma subtypes.

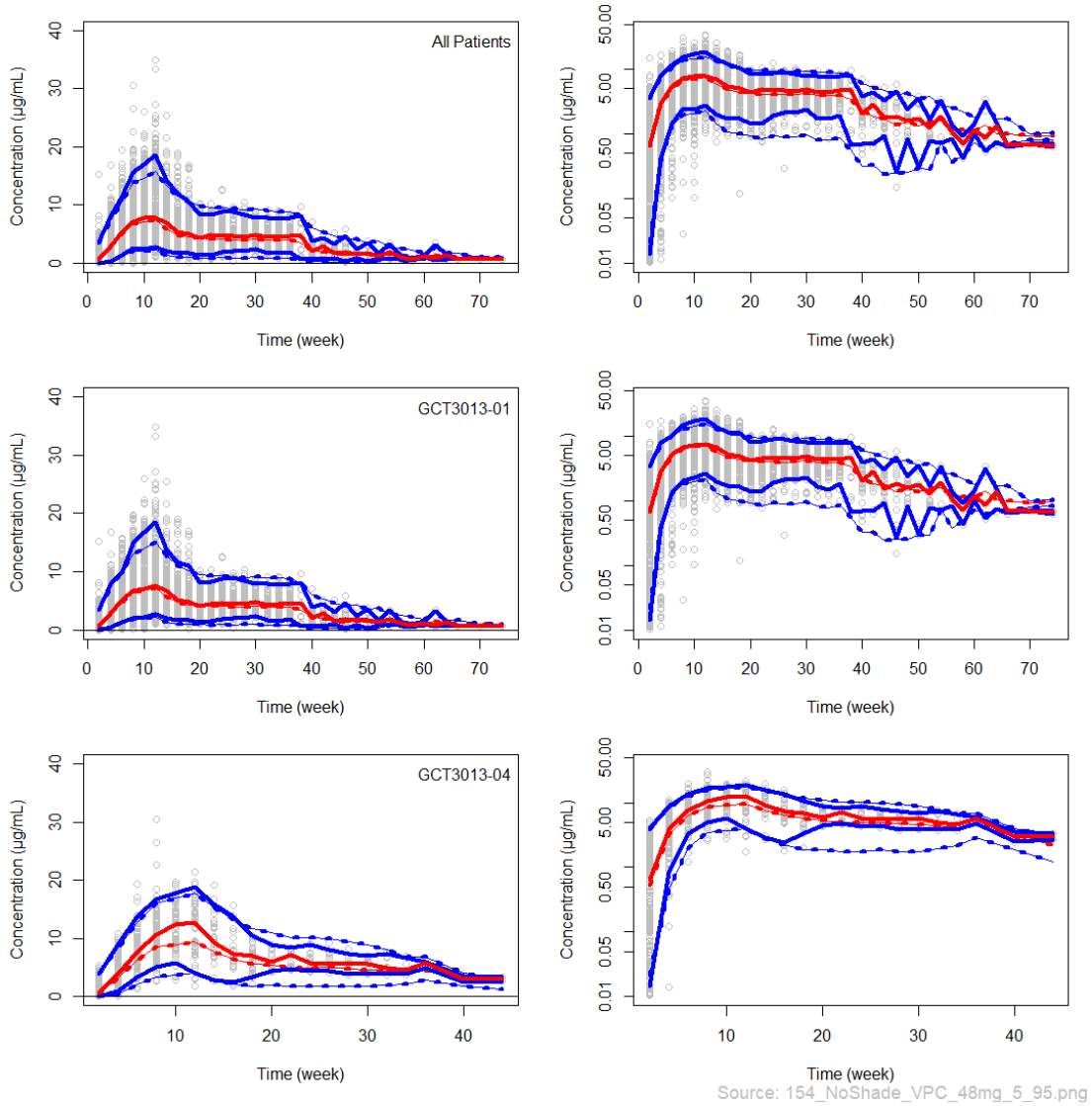
Source: 154cond_parameterSummary_DLBCL_01.csv, 154cond_parameterSummaryDis1Study.csv (Compute_Nominal_48mg_Exposure.R)

Figure 19: Applicant – Main Goodness-of-Fit Plots, Final Model 154, All Data



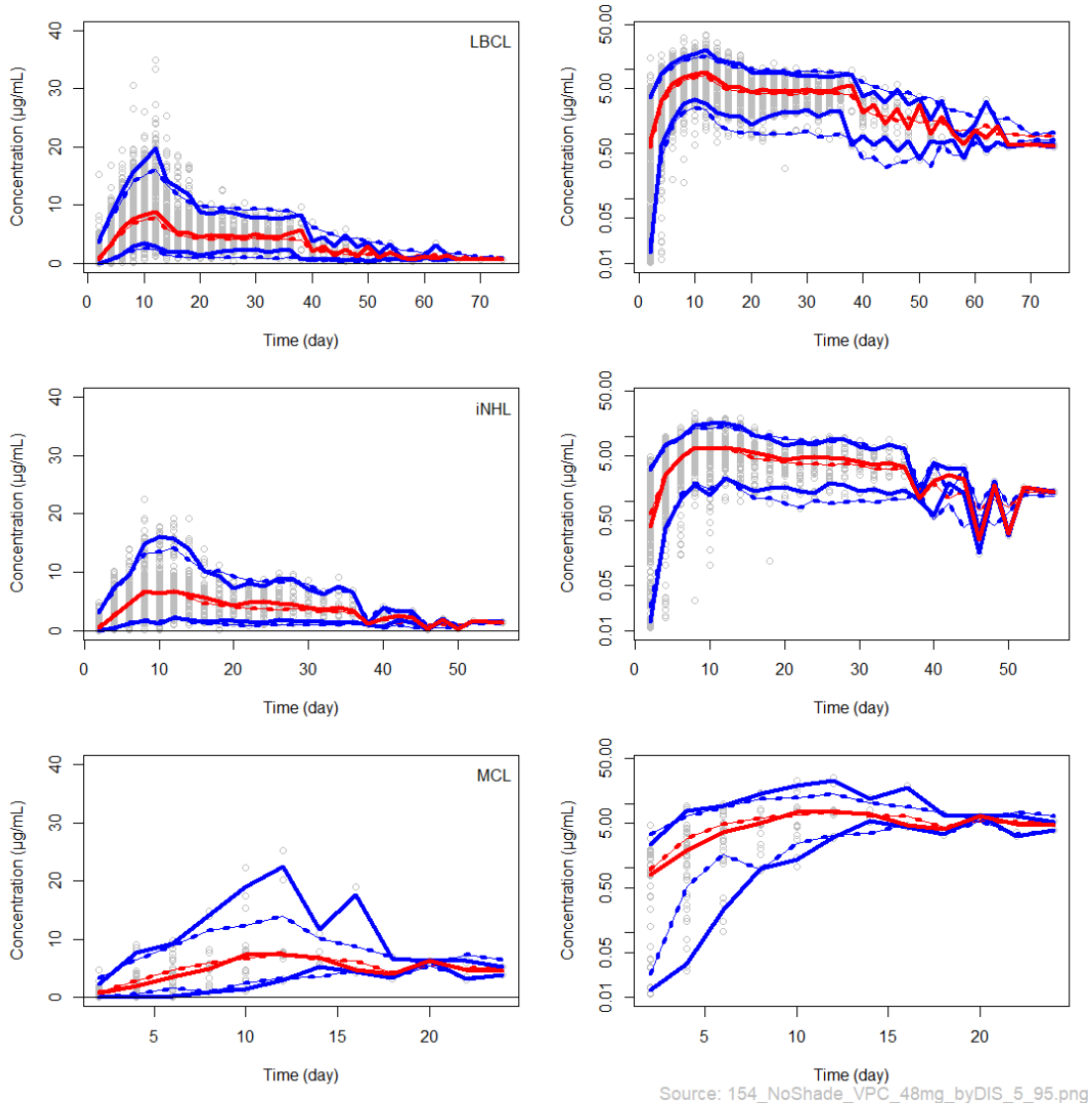
Abbreviations: CWRES = conditional weighted residuals; DV = observed concentrations; IPRED = individual predictions of the model; PRED = population predictions of the model; TIME = time after the first dose. The gray solid y=x or y=0 lines are included for reference. The bold red lines are the lowess (local regression smoother) trend lines.

Figure 20: Applicant – Visual Predictive Check for Observations Following 48 mg Doses, Final Model 154



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 trials with dosing, sampling, and the covariate values of the analysis dataset. Time is time after the first dose.

Figure 21: Visual Predictive Check for Observations Following 48 mg Doses, By Lymphoma Subtypes, Final Model 154



Source: 154_NoShade_VPC_48mg_byDIS_5_95.png

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 trials with dosing, sampling, and the covariate values of the analysis dataset. Time is time after the first dose.

The FDA's Assessment:

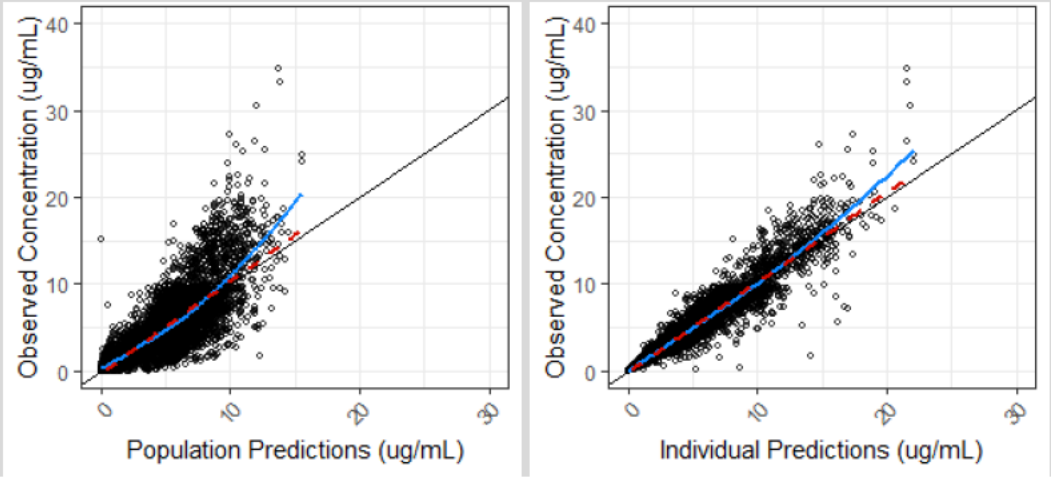
The final PPK model generally adequately characterizes epcoritamab PK, but the model may under-estimate higher concentrations. The model-predicted AUC and C_{trough} are adequate for evaluation of exposure and E-R analyses, but C_{max} is likely less accurate. The PPK analysis does not support the need for dosage adjustments according to any investigated covariate.

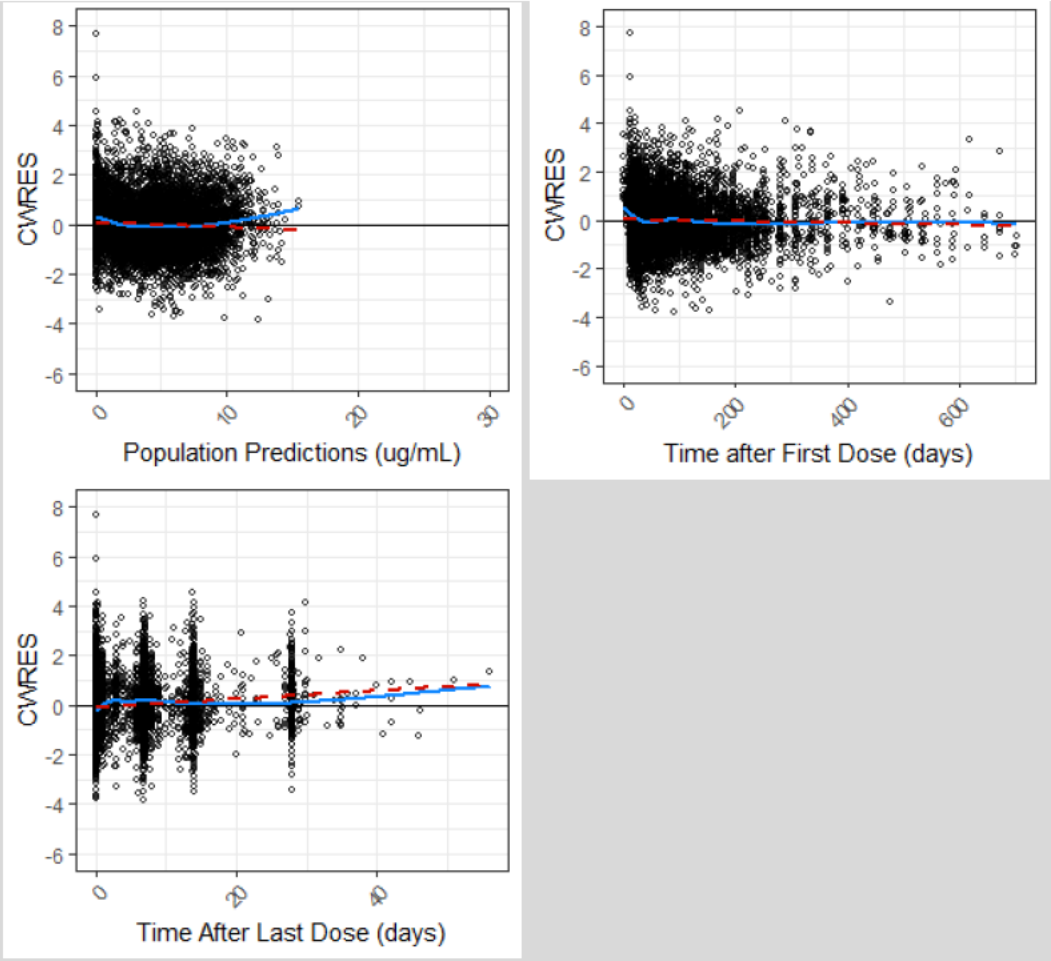
The PPK data used as input to develop the PPK model are described in the PPK Assessment

Summary above. The ECLIA-139 assay was to measure all PK samples included in the PPK analysis. The Reviewer was able to run the final popPK model without significant discrepancies from the results reported in Table 95. The parameters with the highest IIV were Vp (138%), Kss (85%), and Q (87%).

Goodness-of-fit plots indicate that the PPK model is able to adequately characterize epcoritamab concentrations from approximately 0.1 ug/mL up to 15 ug/mL. The model under-estimates epcoritamab concentrations below approximately 0.1 ug/mL (see Figure 19), possibly related to exclusion of BLQ data from the model input. The model also under-estimated concentrations of 15 ug/mL and above, as evident in the goodness-of-fit plot of IPRED versus DV on a linear scale (Figure 22) and the VPC plot (Figure 20 and Figure 21Figure 21). Therefore, model-predicted C_{max} may be lower than true C_{max}. Model-predicted exposure metrics of C_{trough}, C_{avg}, and AUC are likely more accurate than C_{max}. The model-predicted C_{max} may be adequate for exploratory evaluation of relative exposure differences according to subgroups, but the magnitude of difference and individual model-predicted C_{max} values may be lower than true C_{max}.

Figure 22: Goodness of Fit Plots, Final Model, Linear Scale





Loess in solid blue; Linear regression in dashed red. The lower limit of quantification (LLOQ) for observed PK samples was 0.01 ug/mL. CWRES = conditional weighted residual; TAD = time after dose.
Source: Reviewer analysis

The model's under-estimation of higher concentrations may be related to the limited sampling timepoints in Study GCT3013-01 and GCT3013-04. The majority of PK samples in the PPK analysis were measured shortly before the next SC dose or shortly after (i.e., <12 hours) SC dose administration when concentrations would be relatively low. The PPK analysis indicates that median T_{max} occurs between 2.3 to 5.0 days (range of 0.3 to 7 days) after SC administration of 48 mg epcoritamab (Table 96). However, the Applicant's PPK dataset indicates that only 177/6819 (2.6%) PK samples in the analysis were collected between 2 to ≤5 days after last dose (Table 97). The PK sampling schedule did not measure PK around the time of peak concentration in most or all patients. Additional PK data closer to T_{max} would likely improve the model fit at higher concentrations.

Table 96: Model-Predicted Epcoritamab Tmax Over Time Following Proposed Dosage Regimen in Patients with PK Data

Parameter	Statistic	First Step-Up Dose (0.16 mg; Week 1)	Second Step-Up Dose (0.8 mg; Week 2)	First full 48 mg dose (Week 3)	Second full 48 mg dose (Week 4)	Week 12 48 mg full dose	Week 13 48 mg full dose
T_{max} (days)	Median	5.0	4.7	4.1	3.0	2.3	2.3
	Min, Max	0.3, 7.0	0.3, 7.0	0.3, 7.0	0.3, 7.0	0.3, 3.3	0.3, 3.2

Data shown for simulation of proposed epcoritamab dosing (i.e., 0.16/0.8/48 mg then 48 mg QW in Cycles 1 to 3, 48 mg Q2W in Cycles 4 to 9, and 48 mg Q4W in Cycle 10 and beyond) in 327 patients from GCT3013-01 and GCT3013-04 with quantifiable PK concentration data. 1 cycle = 28 days.
F = absolute bioavailability following subcutaneous administration.
Source: Reviewer analysis of Applicant's dataset

Table 97: Timing of PK Samples Included in PPK Analysis

	Number of PK Samples in the PPK Analysis			
Time After Last Dose	GCT3013-01 dose escalation	GCT3013-01 expansion	GCT3013-04	TOTAL
<12 hours	428	2255	205	**2888**
12 to <24 hours	31	204	66	**301**
1 to <2 days	16	27	18	**61**
2 to <3 days	61	27	15	**103**
3 to <4 days	18	5	19	**42**
4 to <5 days	5	10	17	**32**
5 to <6 days	13	59	26	**98**
6 to <7 days	92	1063	346	**1501**
7 days or more	328	1164	301	**1793**

Note: data shown for quantifiable PK samples included in the PPK analysis. PK samples below the LLOQ were not included as input in the PPK analysis.
Source: Reviewer's analysis of Applicant's PPK dataset ("nonmemdatafinal.xpt")

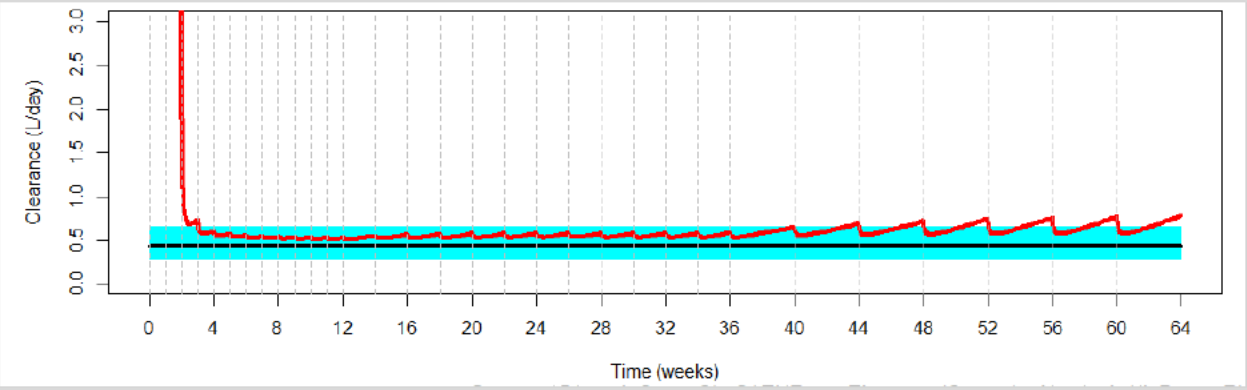
The final epcoritamab model used a quasi-steady-state approximation of a target-mediated drug disposition model structure (Gibiansky et al. 2008). Elimination half-life is summarized in Table 98. Total apparent clearance (CL/F) was equal to the sum of target-mediated CL/F and target-independent CL/F. Median total CL/F decreases as epcoritamab concentrations increase over time, as shown in Figure 23. The geometric mean (CV%) apparent total clearance is 3.34 L/day (102%) at the first full treatment dose and 0.53 L/day (39.7%) at the 11th full dose. Median target-mediated CL/F was between 85 to 90% of total CL/F during administration of the proposed priming dose, intermediate dose, and first full dose. By Week 12, target-mediated CL/F was <15% of total CL/F.

Table 98: Model-Predicted Epcoritamab Elimination Half Life Following Proposed Dosage Regimen in Patients with PK Data

Statistic	End of Cycle 3 (i.e., end of QW dosing window)	End of Cycle 9 (i.e., end of Q2W dosing window)	Steady state with Q4W dosing*
Geometric mean (CV%)	22.0 days (58%)	24.4 days (72%)	22.2 days (75%)

* Steady state values are approximated at Cycle 15 (Week 60).
Data shown for simulation of proposed epcoritamab dosage (i.e., 0.16/0.8/48 mg then 48 mg QW in Cycles 1 to 3, 48 mg Q2W in Cycles 4 to 9, and 48 mg Q4W in Cycle 10 and beyond) in 327 patients with B-cell NHL from GCT3013-01 and GCT3013-04 with quantifiable PK.
CV = coefficient of variation; QW = once weekly; Q2W = once every 2 weeks; Q4W = once every 4 weeks.
Source: Table 30 in Applicant's PopPK/E-R Report

Figure 23: Total Apparent Clearance Over Time Following Proposed Dosing Schedule

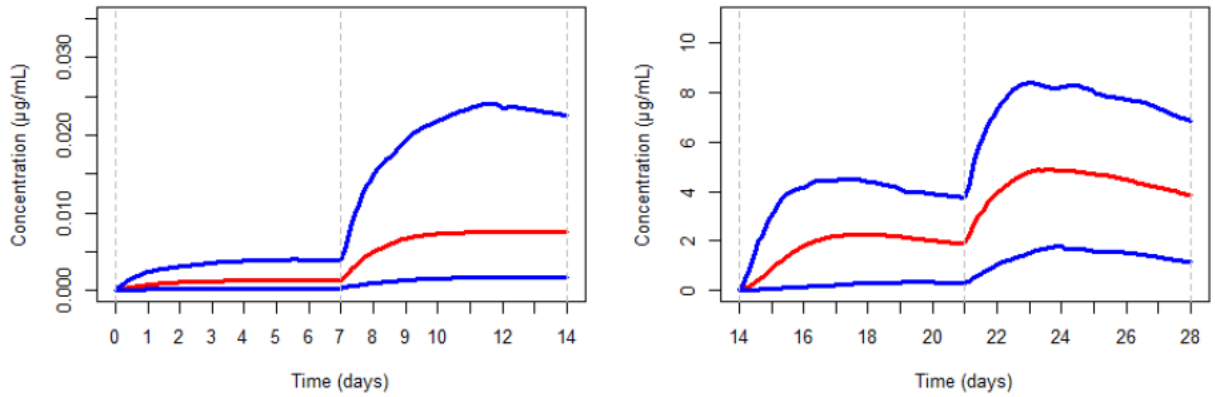


Data shown for simulation of proposed epcoritamab dosage (i.e., 0.16/0.8/48 mg then 48 mg QW in Cycles 1 to 3, 48 mg Q2W in Cycles 4 to 9, and 48 mg Q4W in Cycle 10 and beyond) in 327 patients with B-cell NHL from GCT3013-01 and GCT3013-04 with quantifiable PK. Red line = median total epcoritamab clearance. Black line = median time-and-concentration-independent clearance. Blue shaded area = 90% prediction interval of time-and-concentration-independent clearance.
QW = once weekly; Q2W = once every 2 weeks; Q4W = once every 4 weeks.
Source: Figure 7 in Applicant's PopPK/E-R Report

The model-predicted median PK profile following proposed epcoritamab dosage is displayed for Cycle 1 in Figure 24 and up to Week 64 in Figure 25.

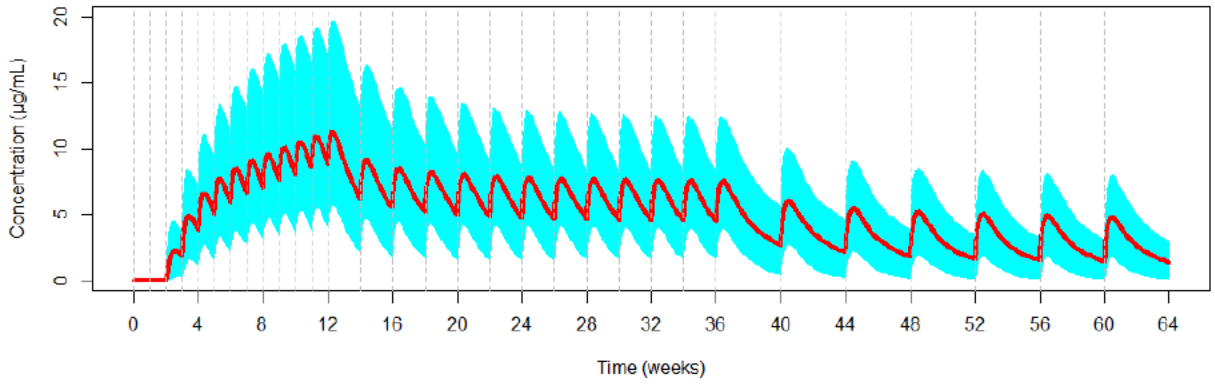
Table 99 summarizes exposure at the end of the QW, Q2W, and Q4W dosing regimens. Exposure according to study and disease subtype is summarized for Cycle 1 in Table 100 and by dose event in Table 101.

Figure 24: Model-predicted Cycle 1 Median Epcoritamab Concentration over time following proposed dosing schedule



Data shown for simulation of proposed epcoritamab dosage (i.e., 0.16/0.8/48 mg then 48 mg QW in Cycles 1 to 3, 48 mg Q2W in Cycles 4 to 9, and 48 mg Q4W in Cycle 10 and beyond) in 327 patients with B-cell NHL from GCT3013-01 and GCT3013-04 with quantifiable PK concentration data. Red solid line = median predicted epcoritamab concentration. Blue solid line = 5th to 95th percentile interval of predicted epcoritamab concentration. The lower limit of quantification (LLOQ) for observed PK samples was 0.01 ug/mL.
QW = once weekly; Q2W = once every 2 weeks; Q4W = once every 4 weeks.
Source: figure generated by Reviewer from Applicant's dataset ("154_SimulationDataStudy.csv"), Applicant's model file ("154cond-ctl.txt"), and Applicant's code ("compute-nominal-48mg-exposure.r").

Figure 25: Model-predicted Median Epcoritamab Concentration over time following proposed dosing schedule



Data shown for simulation of proposed epcoritamab dosage (i.e., 0.16/0.8/48 mg then 48 mg QW in Cycles 1 to 3, 48 mg Q2W in Cycles 4 to 9, and 48 mg Q4W in Cycle 10 and beyond) in 327 patients with B-cell NHL from GCT3013-01 and GCT3013-04 with quantifiable PK concentration data. Red line = median predicted epcoritamab concentration. Blue shaded area = 5th to 95th percentile interval of predicted epcoritamab concentration. The lower limit of quantification (LLOQ) for observed PK samples was 0.01 ug/mL.
QW = once weekly; Q2W = once every 2 weeks; Q4W = once every 4 weeks.
Source: Figure 7 in Applicant's PopPK/E-R Report

Table 99: Geometric Mean Exposure for Proposed QW, Q2W, and Q4W Dosage Regimen

	Statistic	Week 3 up to Week 4	Week 12 up to Week 13	Week 35 up to Week 37	Week 57 up to Week 60
		First Full Dose	Last Full Dose in QW Regimen	Last Full Dose in Q2W Regimen	Last Full Dose in Q4W Regimen
$AUC_{0\text{-}tau}$ (ug/mL*day)	Geometric Mean (CV%)	9.82 (116%)	69.3 (43.7%)	82.6 (51.3%)	72.5 (75.5%)
C_{avg} (ug/mL)	Geometric Mean (CV%)	1.4 (116%)	9.9 (43.7%)	5.9 (51.3%)	2.59 (75.5%)
C_{max} (ug/mL)	Geometric Mean (CV%)	1.89 (111%)	10.8 (40.7%)	7.47 (44.1%)	4.59 (62.1%)
C_{trough} (ug/mL)	Geometric Mean (CV%)	1.5 (107%)	8.51 (50.6%)	4.11 (70.9%)	1.17 (126%)

Data shown for simulation of proposed epcoritamab dosage (i.e., 0.16 mg on the first day of Week 1, 0.8 mg on the first day of Week 2, then 48 mg on the first day of Weeks 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 41, 45, 49, 53, and 57) in 327 patients from GCT3013-01 and GCT3013-04 with quantifiable PK concentration data.
$AUC_{0\text{-}tau}$ = area under the concentration versus time curve from the time of dose administration to the end of the dosing interval (i.e., 7 days, 14 days, or 28 days post-dose for QW, Q2W, and Q4W regimens, respectively);
C_{avg} = average concentration over the dosing interval; C_{trough} = concentration at the end of the dosing interval;
CV = coefficient of variation; QW = once weekly; Q2W = once every 2 weeks; Q4W = once every 4 weeks.
Source: Table 30 in Applicant's PopPK/E-R Report

Table 100: Epcoritamab Exposure in Cycle 1 By Study and Disease Subtype Following Proposed Dosage Regimen

Metric	Statistic	GCT3013-01 LBCL (n=170)	GCT3013-01 iNHL (n=79)	GCT3013-01 MCL (n=18)	GCT3013-04 LBCL (n=42)	GCT3013-04 iNHL (n=18)
Cycle 1 AUC (ug/mL*day)	Geo Mean (CV%)	41.1 (52.2%)	25.3 (110.1%)	22.5 (197.0%)	53.3 (36.5%)	50.7 (31.2%)
	Geo Mean 95% CI	38.1 - 44.2	20.7 - 30.9	12 - 42.1	47.8 - 59.5	43.5 - 59.0
	Median	44.1	31.5	35.6	58.5	55.6
	5^{th} to 95^{th} percentile	16.1 - 79.7	2.73 - 64	1.59 - 68.1	33.3 - 86.5	30.6 - 76.4
	Min - Max	6.59 - 123.4	0.881 - 92.1	0.681 - 71.7	16.0 - 91.8	29.6 - 80.6
Cycle 1 C_{avg} (ug/mL)	Geo Mean (CV%)	1.47 (52.2%)	0.903 (110.1%)	0.804 (197.0%)	1.9 (36.5%)	1.81 (31.2%)
	Geo Mean 95% CI	1.36 - 1.58	0.74 - 1.1	0.43 - 1.5	1.71 - 2.13	1.56 - 2.11
	Median	1.58	1.12	1.27	2.09	1.99
	5th to 95th percentile	0.575 - 2.85	0.09764 - 2.29	0.05664 - 2.43	1.19 - 3.09	1.09 - 2.73
	Min - Max	0.235 - 4.41	0.03147 - 3.29	0.02433 - 2.56	0.572 - 3.28	1.06 - 2.88

Data shown for simulation of proposed epcoritamab dosage in Cycle 1 (i.e., 0.16/0.8/48 mg then 48 mg QW) in 327 patients with B-cell NHL from GCT3013-01 and GCT3013-04 with quantifiable PK concentration data.
$AUC_{0\text{-}tau}$ = area under the concentration versus time curve from the time of dose administration to the end of the dosing interval (i.e., 7 days, 14 days, or 28 days post-dose for QW, Q2W, and Q4W regimens, respectively);
C_{avg} = average concentration over the dosing interval; C_{trough} = concentration at the end of the dosing interval;
CV = coefficient of variation; iNHL = indolent non-Hodgkin lymphoma; LBCL = large B-cell lymphoma; MCL = mantle cell lymphoma; QW = once weekly; Q2W = once every 2 weeks; Q4W = once every 4 weeks.
Source: Reviewer analysis of Applicant's dataset and Table 31 in Applicant's PopPK/E-R Report

Table 101: Epcoritamab Exposure Per Dose Event By Study and Disease Subtype Following Proposed Dosage Regimen in Patients with PK Data

Cycle	Metric	Statistic	GCT3013-01 LBCL (n=170)	GCT3013-01 iNHL (n=79)	GCT3013-01 MCL (n=18)	GCT3013-04 LBCL (n=42)	GCT3013-04 iNHL (n=18)
First Step-Up Dose (0.16 mg; Week 1)	$AUC_{0\text{-}tau}$ (ug/mL*day)	Geo Mean (CV%)	0.00825 (74.4%)	0.0047 (128.1%)	0.00523 (153.2%)	0.01003 (76.7%)	0.00711 (100.5%)
		Geo Mean 95% CI	0.00746 - 0.00912	0.00377 - 0.00586	0.00303 - 0.00903	0.00811 - 0.01239	0.00469 - 0.01077
		Median	0.00799	0.0057	0.00703	0.01086	0.0073
		Min - Max	0.00113 - 0.05985	0.00027 - 0.03162	0.00029 - 0.01929	0.00134 - 0.03423	0.00212 - 0.03617
	C_{trough} (ug/mL)	Geo Mean (CV%)	0.00135 (72.4%)	0.0008 (121.2%)	0.00085 (147.9%)	0.00166 (77.4%)	0.00122 (100.9%)
		Geo Mean 95% CI	0.00123 - 0.00149	0.00065 - 0.00099	0.0005 - 0.00146	0.00134 - 0.00206	0.00081 - 0.00185
		Median	0.00135	0.00091	0.00112	0.00176	0.00133
		Min - Max	0.00017 - 0.00873	0.00005 - 0.00476	0.00005 - 0.00297	0.00028 - 0.0059	0.00037 - 0.00661
Second Step-Up Dose (0.8 mg; Week 2)	$AUC_{0\text{-}tau}$ (ug/mL*day)	Geo Mean (CV%)	0.05124 (74.5%)	0.02927 (127.2%)	0.03223 (153.7%)	0.06276 (76.5%)	0.04465 (100.6%)
		Geo Mean 95% CI	0.04634 - 0.05666	0.0235 - 0.03646	0.01864 - 0.05573	0.0508 - 0.07755	0.02946 - 0.06766
		Median	0.05079	0.03492	0.04362	0.06749	0.04593
		Min - Max	0.00673 - 0.363	0.0017 - 0.197	0.00175 - 0.115	0.00877 - 0.213	0.01326 - 0.226
	C_{trough} (ug/mL)	Geo Mean (CV%)	0.00806 (73.3%)	0.00475 (121.5%)	0.00506 (149.3%)	0.00996 (77.7%)	0.00734 (100.7%)
		Geo Mean 95% CI	0.0073 - 0.0089	0.00384 - 0.00588	0.00295 - 0.00867	0.00804 - 0.01233	0.00484 - 0.01113
		Median	0.00795	0.00529	0.00664	0.01057	0.00792
		Min - Max	0.00095 - 0.05149	0.00029 - 0.02821	0.00028 - 0.01707	0.00167 - 0.03487	0.00221 - 0.03887
First full 48 mg dose (Week 3)	$AUC_{0\text{-}tau}$ (ug/mL*day)	Geo Mean (CV%)	11.5 (72.4%)	5.9 (181.1%)	5.52 (266.0%)	15.3 (58.4%)	13 (57.6%)
		Geo Mean 95% CI	10.4 - 12.7	4.5 - 7.73	2.69 - 11.3	12.9 - 18.1	9.94 - 16.9
		Median	13.1	8.44	9.45	17.1	16.2
		Min - Max	0.807 - 38	0.169 - 28.6	0.14 - 25.2	1.49 - 29.6	4.33 - 26.6
	C_{trough} (ug/mL)	Geo Mean (CV%)	1.72 (74.0%)	0.932 (153.3%)	0.852 (228.6%)	2.34 (52.0%)	2.16 (47.1%)
		Geo Mean 95% CI	1.55 - 1.9	0.729 - 1.19	0.435 - 1.67	2.01 - 2.72	1.73 - 2.69
		Median	1.94	1.27	1.31	2.54	2.63
		Min - Max	0.11 - 6.80	0.03416 - 5.11	0.02391 - 3.50	0.425 - 4.69	0.914 - 4.01
Second full 48 mg dose (Week 4)	$AUC_{0\text{-}tau}$ (ug/mL*day)	Geo Mean (CV%)	29.2 (47.6%)	18.8 (99.3%)	16.5 (185.2%)	37.4 (32.7%)	37.1 (25.1%)
		Geo Mean 95% CI	27.2 - 31.2	15.6 - 22.7	9.02 - 30.3	33.9 - 41.3	32.9 - 42
		Median	31.2	23.9	26.6	39.3	39.8
		Min - Max	5.31 - 85.4	0.684 - 63.3	0.54 - 46.4	14.5 - 62.2	23.6 – 54.0
		Geo Mean (CV%)	3.59 (58.3%)	2.38 (90.7%)	2.15 (170.2%)	4.78 (36.6%)	4.97 (24.7%)

Cycle	Metric	Statistic	GCT3013-01 LBCL (n=170)	GCT3013-01 iNHL (n=79)	GCT3013-01 MCL (n=18)	GCT3013-04 LBCL (n=42)	GCT3013-04 iNHL (n=18)
	C_{trough} (ug/mL)	Geo Mean 95% CI	3.31 - 3.9	2 - 2.83	1.2 - 3.84	4.28 - 5.34	4.41 - 5.61
		Median	3.97	3.02	2.85	4.67	5.31
		Min - Max	0.36 - 12.8	0.12 - 9.01	0.07472 - 6.2	2.15 - 8.65	2.97 - 7.57
Week 12 Full Dose (48mg) (last week of QW dosage)	$AUC_{0\text{-}tau}$ (ug/mL*day)	Geo Mean (CV%)	68.9 (45.1%)	56.9 (35.7%)	65.5 (43.1%)	89.9 (34.3%)	99.6 (19.8%)
		Geo Mean 95% CI	64.6 - 73.6	52.7 - 61.5	53.4 - 80.5	81.1 - 99.8	90.4 - 109.8
		Median	72.0	61.2	68.1	97.0	96.2
		Min - Max	7.41 - 236.2	21.4 - 137.5	21.2 - 140.3	37.6 - 209.4	68.6 - 148.6
	C_{trough} (ug/mL)	Geo Mean (CV%)	8.41 (53.3%)	6.94 (41.2%)	8.12 (48.1%)	11.2 (39.5%)	12.7 (21.8%)
		Geo Mean 95% CI	7.79 - 9.07	6.35 - 7.58	6.47 - 10.2	9.98 - 12.7	11.4 - 14.2
		Median	8.96	7.54	8.51	12.1	12.4
		Min - Max	0.491 - 31.9	2.13 - 18	2.23 - 18.6	3.75 - 27.6	8.69 - 20.0

Data shown for simulation of proposed epcoritamab dosing (i.e., 0.16/0.8/48 mg then 48 mg QW in Cycles 1 to 3, 48 mg Q2W in Cycles 4 to 9, and 48 mg Q4W in Cycle 10 and beyond) in 327 patients with B-cell NHL from GCT3013-01 and GCT3013-04 with quantifiable PK concentration data. The lower limit of quantification (LLOQ) for observed PK samples was 0.01 ug/mL.

$AUC_{0\text{-}tau}$ = area under the concentration versus time curve from the time of dose administration to the end of the dosing interval (i.e., 7 days, 14 days, or 28 days post-dose for QW, Q2W, and Q4W regimens, respectively); C_{avg} = average concentration over the dosing interval; C_{trough} = concentration at the end of the dosing interval; CV = coefficient of variation; iNHL = indolent non-Hodgkin lymphoma; LBCL = large B-cell lymphoma; MCL = mantle cell lymphoma; QW = once weekly; Q2W = once every 2 weeks; Q4W = once every 4 weeks.

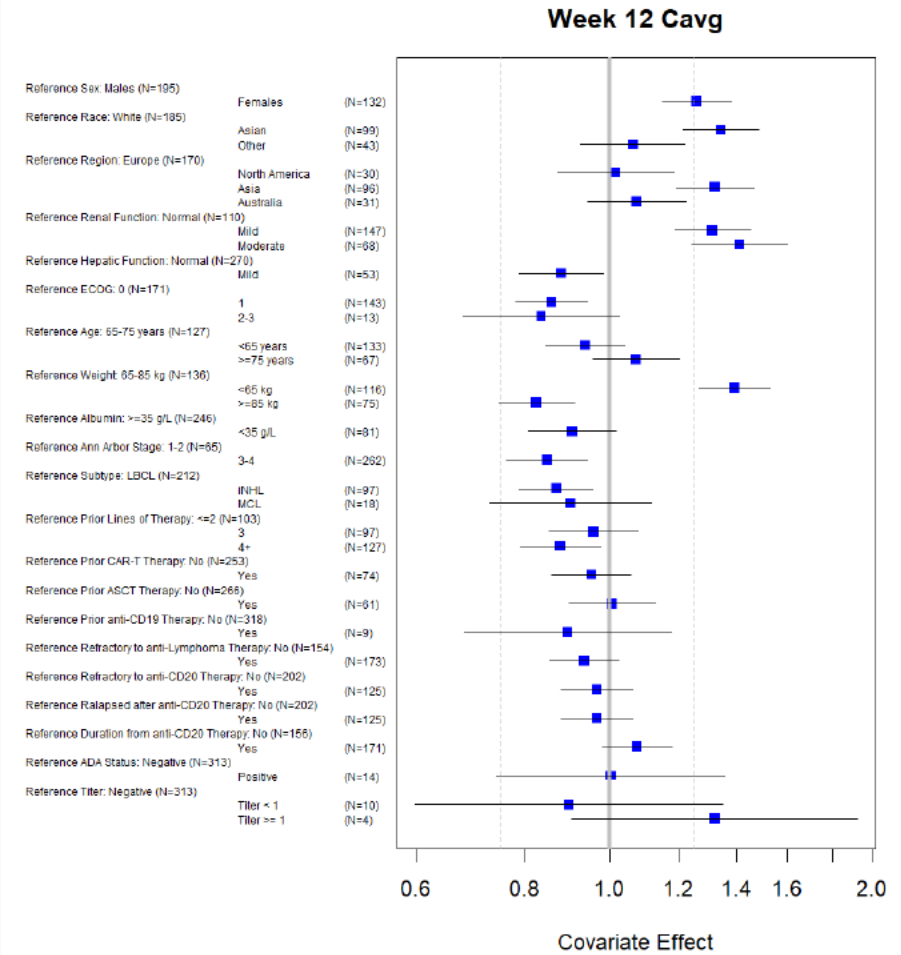
Source: Reviewer analysis of Applicant's dataset and Table 31 in Applicant's PopPK/E-R Report

Based on PPK analysis, dosage adjustment is not recommended according to body weight, age, sex, White or Asian racial category, mild to moderate renal impairment (CLcr ≥30 mL/min to <90 mL/min), or mild hepatic impairment (total bilirubin ≤ULN and AST >ULN, or total bilirubin 1 to 1.5 times ULN and any AST). The effects of severe renal impairment (CLcr <30 mL/min), end-stage renal disease, and moderate to severe hepatic impairment (total bilirubin >1.5 times ULN and any AST) on the PK of epcoritamab are unknown.

According to the racial category information in the Applicant's popPK dataset, PK data were available for 185 White patients (57%), 99 Asian patients (30%), 1 Native Hawaiian or Other Pacific patient (0.3%), and 42 patients with race recorded as "missing, other, or not reported" (13%). Therefore, data were inadequate to assess the impact of racial categories other than White or Asian on PK.

Relative exposure differences following the proposed dosage regimen are presented in Figure 9 in Section 6.3.2.3 for Cycle 1 AUC and in Figure 26 for Week 12 C_{avg}.

Figure 26: Predicted Geometric Mean Epcoritamab Week 12 Cavg: by Covariates, Relative to Reference Group

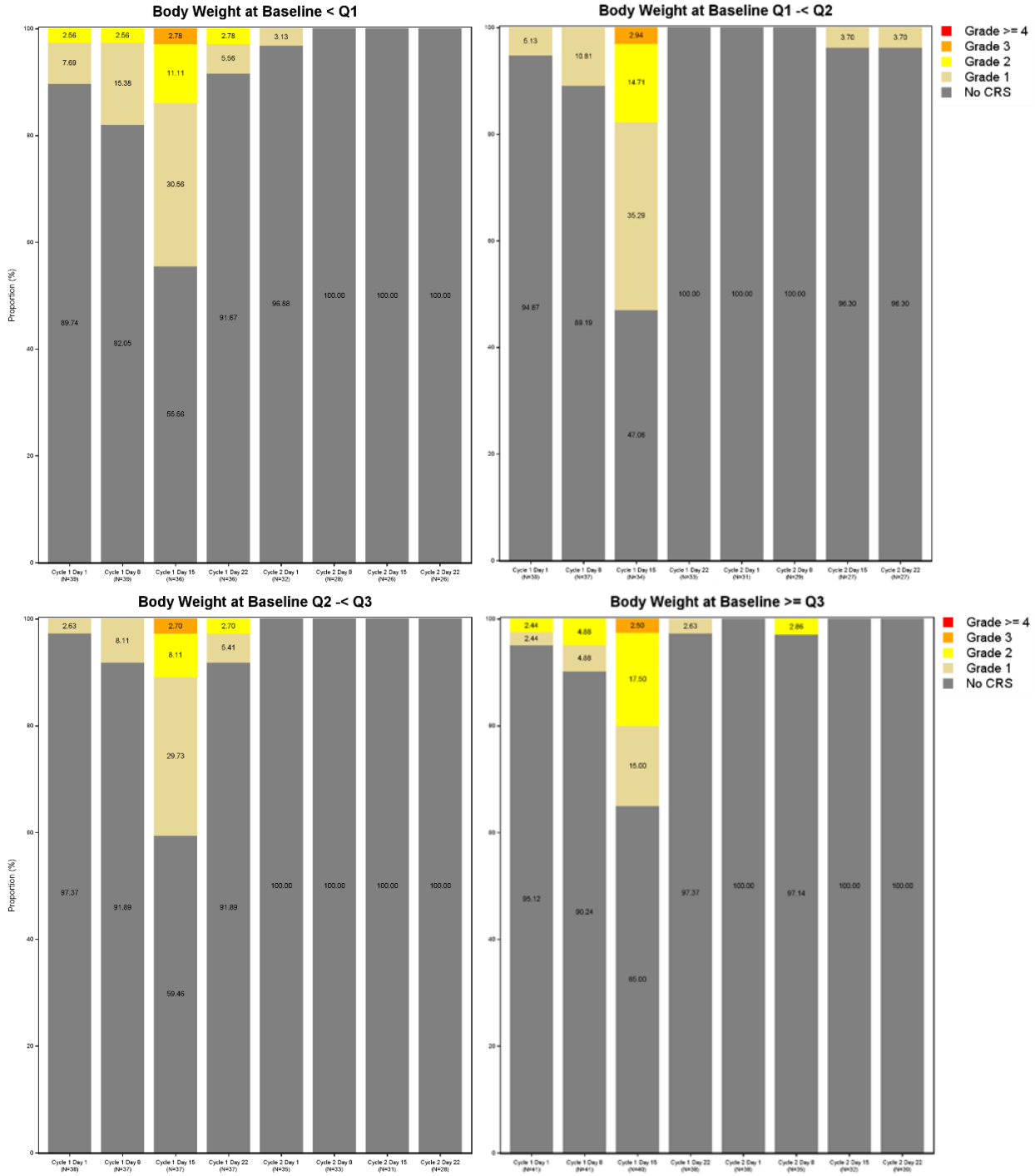


Note: Covariate effect (x-axis) is a log scale. Blue square = geometric mean. Horizontal black error bars = 95% confidence interval of the geometric mean. Dashed vertical reference lines represent 25% lower and 25% higher geometric mean Cycle 1 AUC relative to the reference group.
ADA = antidrug antibodies; ASCT = autologous stem cell transplant; CAR-T = chimeric antigen receptor T cell; C_{avg} = average concentration; CD = cluster of differentiation; ECOG = Eastern Cooperative Oncology Group; LBCL = large B-cell lymphoma.
Source: Figure 68 in Applicant's PopPK/E-R Report

Higher body weight was associated with lower epcoritamab exposure. In B-NHL patients with PK data who received the recommended dosage of epcoritamab (n=325), Cycle 1 median AUC was 13% lower in the higher body weight (BW) group (85 kg and above) and 37% higher in the lower BW group (less than 65 kg) compared to patients with BW of 65 to <85 kg. In patients with R/R LBCL (n=212), Cycle 1 geometric mean AUC was 18% lower in the higher BW group (85 kg and above) and 32% higher in the lower BW group (less than 65 kg) compared to patients with BW of 65 to less than 85 kg.

The subgroup analysis did not identify any associations between body weight subgroup and TEAE incidence or severity (refer to Section 7.1.4 of the Applicant's Summary of Clinical Safety). Incidence and severity of CRS at each dose event also did not differ significantly across weight quartiles, as shown in Figure 27. Therefore, the difference in exposure according to body weight is not expected to have a significant impact on clinical outcomes. No dosage adjustment is recommended according to body weight based on current data.

Figure 27: CRS Events by Body Weight at Baseline in Patients with LBCL (GCT3013-01 LBCL Expansion Part, Full Analysis Set)



Note: Q1 = 62kg, Q2 = 71.5kg, Q3 = 85kg. Data cutoff date: 31 Jan 2022. CRS = cytokine release syndrome; LBCL = large B-cell lymphoma; Q = quartile.
Source: Figure 1 in Applicant's 11 January 2023 response to 09 January 2023 information request

19.4.5. Exposure-Response Analysis

19.4.5.1. ER (efficacy) Executive Summary

The FDA's Assessment:
The E-R efficacy analysis generally supports the proposed full dose of 48 mg. Higher Cycle 1 AUC was associated with better ORR and CR rates in patients with LBCL as well as in patients with DLBCL. The lowest Cycle 1 AUC quartile was associated with worse OS and worse PFS compared to higher quartiles.

19.4.5.2. ER (efficacy) Assessment Summary

The Applicant's Position:

General Information	
Goal of ER analysis	The objectives of the exposure-efficacy analysis were to assess the relationships between epcoritamab exposure and key efficacy endpoints in subjects with LBCL and DLBCL.
Study Included	GCT3013-01 and GCT3013-04
Endpoint	Overall (complete or partial) response rate (ORR) (IRC-assessed per Lugano criteria); Complete response rate (CR) (IRC-assessed per Lugano criteria); Duration of response (DOR) (IRC-assessed per Lugano criteria); Progression-free survival (PFS) (IRC-assessed per Lugano criteria); and Overall survival (OS).
No. of Patients (total, and with individual PK)	234 patients with LBCL
Dose(s) Included	Priming doses of epcoritamab tested include 0.004, 0.0128, 0.04, 0.08, 0.12, and 0.16 mg. Intermediate doses of epcoritamab tested include 0.25, 0.5, 0.8, and 1.6 mg. Full doses of epcoritamab tested include 0.0128, 0.04, 0.12, 0.38, 0.76, 1.5, 3, 6, 12, 24, 48, and 60 mg
Exposure Metrics Explored (range)	Predicted AUC over the first cycle (Cycle 1 AUC)
Covariates Evaluated	Age, Gender, Race, ECOG, Weight, Time from last anti-CD20 therapy till first dose of GEN3013, Prior CART therapy, Prior ASCT, Prior anti-lymphoma therapy status, Most recent prior anti-CD20 therapy status, Ann Arbor Stage, ADA, tumor size

Final Model Parameters	Summary	Acceptability [FDA's comments]
Model Structure	Linear logistic regression model	In 234 patients with LBCL from Studies GCT3013-01 and GCT3013-04 who received individual doses ranging from 0.004 to 60 mg, a higher ORR was associated with higher Cycle 1 AUC, no prior CAR-T therapy, and greater than median duration since prior CD20 therapy
Model Parameter Estimates	Table 102	
Model Evaluation	N/A	
Covariates and Clinical Relevance	The exposure-ORR relationship remained positive and statistically significant after accounting for time from last anti-CD20 therapy until first dose of epcoritamab and prior CAR-T therapy.	

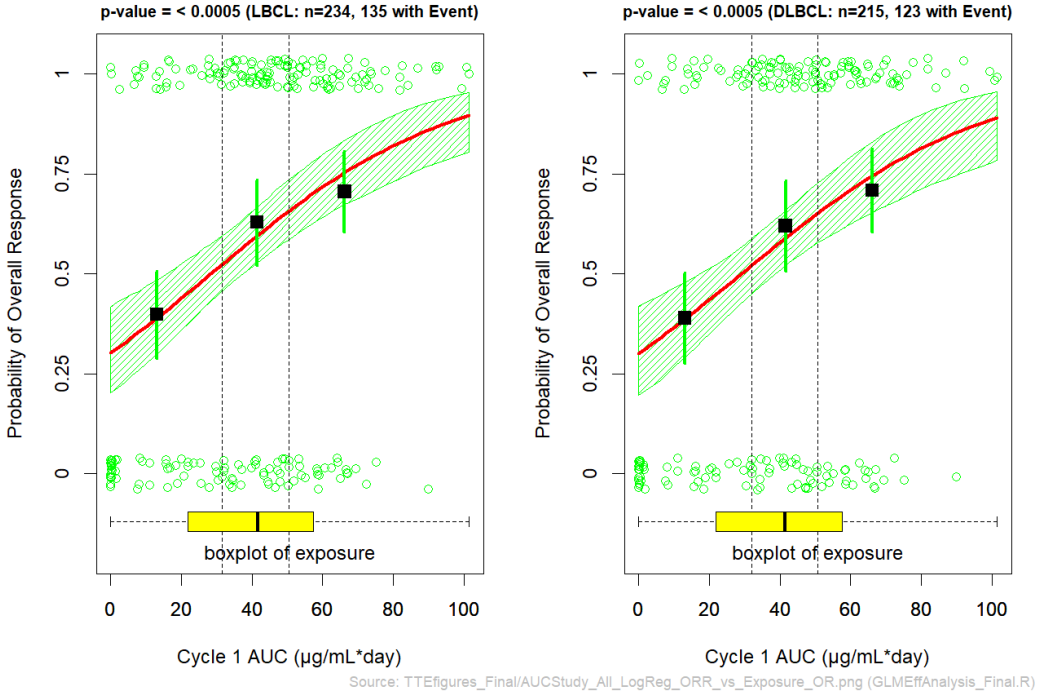
Simulation for Specific Population	N/A	(i.e., greater than 4.8 months) at baseline.
Visualization of E-R relationships	ORR and CR: Figure 28, Figure 29, Figure 30, Figure 31, Figure 32, Figure 33, Figure 34, Figure 35 DOR, PFS, and OS: popPK report Figure 14 to Figure 18 and Figure 105 to Figure 111.	Based on univariate E-R efficacy analysis, higher Cycle 1 AUC was associated with better ORR and better CR. The lowest Cycle 1 AUC quartile appeared to have worse OS (Figure 36) and worse PFS (Figure 37) compared to higher exposure quartiles. No clear E-R associations were identified with duration of response.
Overall Clinical Relevance for ER	Across the full dose range studied (0.004 to 60 mg), statistically significant ($p<0.05$) relationships between key efficacy endpoints (ORR, CR rate, PFS, and OS) and epcoritamab exposure were observed, ie, higher epcoritamab exposures provided higher ORR/CR rate and longer PFS/OS. A similar, numerical trend was also observed for DOR. At the proposed 48 mg full dose (ie, analysis using data only from 48 mg full dose level), exposure-efficacy relationships remained positive for all the key efficacy endpoints and were statistically significant ($p<0.05$) for CR rate. These results indicate that full doses <48 mg are likely to result in compromised efficacy.	The median Cycle 1 AUC following the proposed dosage (i.e., 0.16/0.8/48 mg) is associated with clinical efficacy in terms of ORR and CR rate. Full doses lower than the proposed full dose of 48 mg will likely have lower ORR and CR rates, but the median Cycle 1 AUC following the proposed dosage appears lower than the Cycle 1 AUC value where the E-R efficacy association plateaus. The proposed dosage is acceptable based on the E-R efficacy analysis.
Labeling Language	**Description**	**Acceptability [FDA's comments]**
12.2 Pharmacodynamics	N/A	No E-R efficacy statements are included in the labeling.

Table 102: Applicant – Final Logistic Regression Model for Overall Response: GCT3013-01

Parameter	Coefficient	SE	RSE (%)	95% CI	P value
Intercept	-1.32	0.3494	26.47	-2.005;-0.6349	<0.0005
Exposure	0.04221	0.008688	20.58	0.02518;0.05924	<0.0005
Prior CAR-T therapy	-1.167	0.4022	34.48	-1.955;-0.3782	0.004
DURCDmed	1.458	0.3665	25.14	0.7392;2.176	<0.0005

Abbreviations: CAR-T = chimeric antigen receptor T cell; CI = confidence interval; DURCDmed = elapsed time from prior CD20 therapy at baseline above median; RSE = relative standard error; SE = standard error.
Source: FinalModelGLM_01_AUC_OR.csv (GLMEffAnalysis_Final.R)

Figure 28: Applicant – Logistic Regression for Overall Response: GCT3013-01 and GCT3013-04



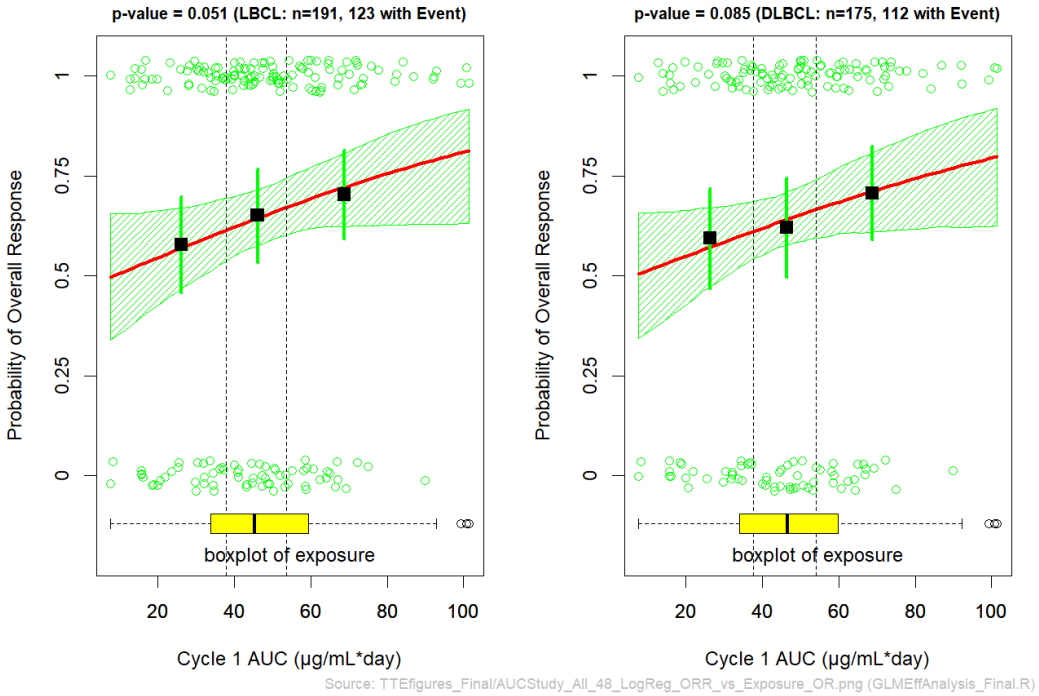
Source: TTEfigures_Final/AUCStudy_All_LogReg_ORR_vs_Exposure_OR.png (GLMEffAnalysis_Final.R)

Abbreviations: AUC = area under the concentration-time curve; DLBCL = diffuse large B-cell lymphoma; LBCL = large B-cell lymphoma; n = number of subjects.

Left: LBCL; right: DLBCL. The red solid line and green shaded area represent the logistic regression model prediction and 95% confidence interval of predictions. Points show exposure of individual subjects with events (p=1) and without events (p=0). Black squares and vertical green lines show observed fraction of subjects with events in each exposure group and 95% confidence interval for these fractions. Dashed vertical lines show bounds of exposure groups. Box plot of exposure is shown by the yellow box with whiskers.

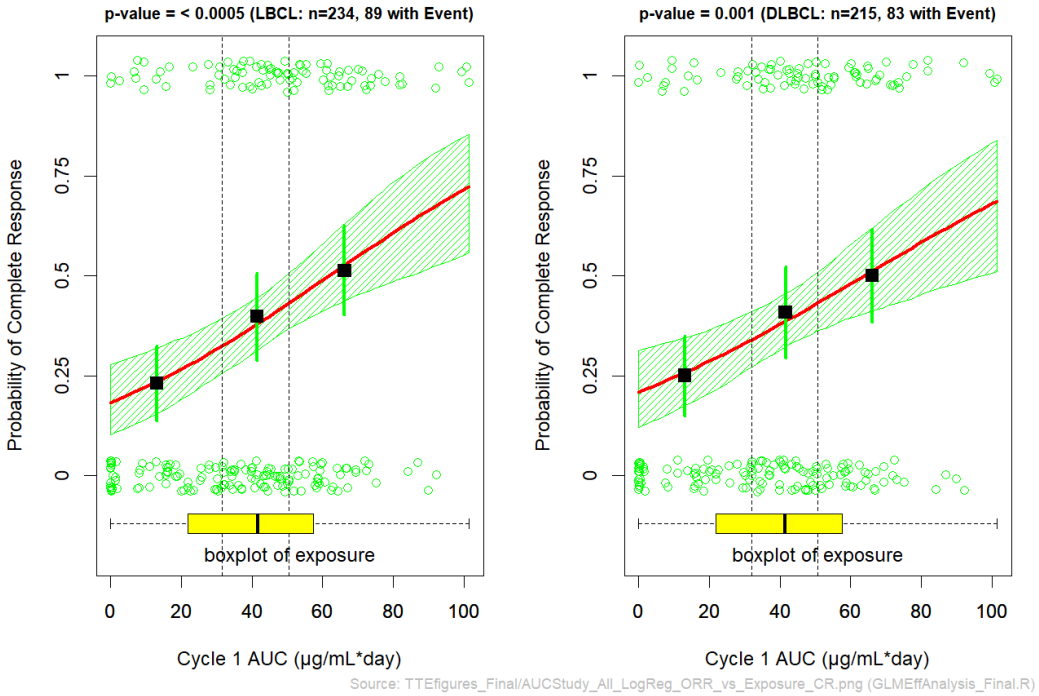
Source: popPK Report Figure 10

Figure 29: Applicant – Logistic Regression for Overall Response: GCT3013-01 and GCT3013-04, Subjects Administered Full Dose of 48 mg



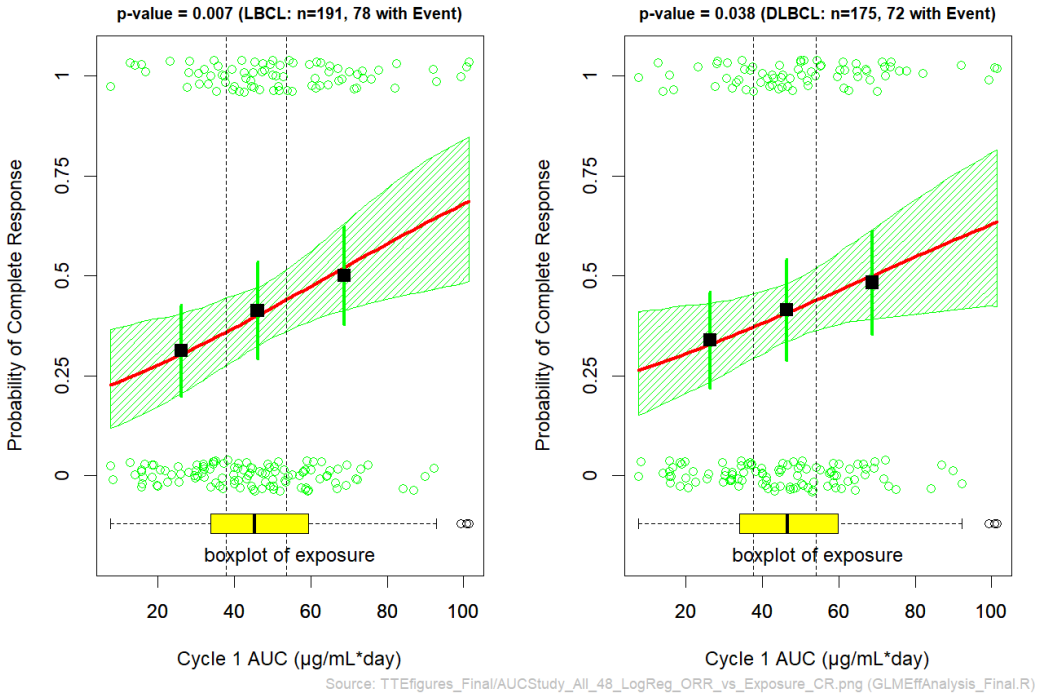
Abbreviations: AUC = area under the concentration-time curve; DLBCL = diffuse large B-cell lymphoma; LBCL = large B-cell lymphoma; n = number of subjects.
Left: LBCL; right: DLBCL. The red solid line and green shaded area represent the logistic regression model prediction and 95% confidence interval of predictions. Points show exposure of individual subjects with events (p=1) and without events (p=0). Black squares and vertical green lines show observed fraction of subjects with events in each exposure group and 95% confidence interval for these fractions. Dashed vertical lines show bounds of exposure groups. Box plot of exposure is shown by the yellow box with whiskers.
Source: popPK Report Figure 11

Figure 30: Applicant – Logistic Regression for Complete Response: GCT3013-01 and GCT3013-04



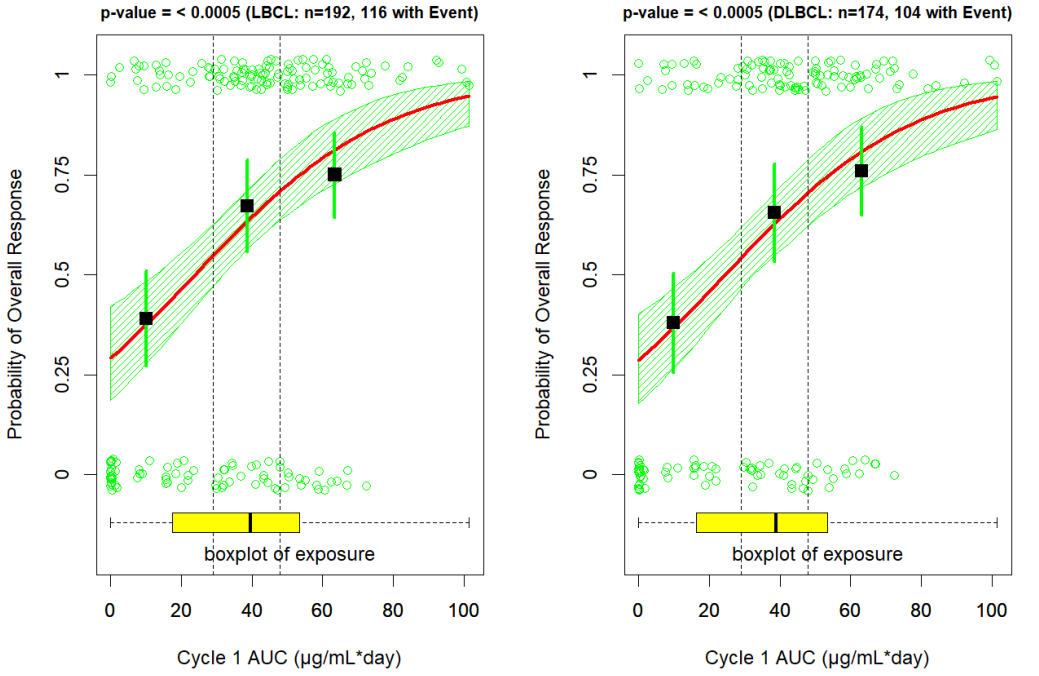
Abbreviations: AUC = area under the concentration-time curve; DLBCL = diffuse large B-cell lymphoma; LBCL = large B-cell lymphoma; n = number of subjects.
Left: LBCL; right: DLBCL. The red solid line and green shaded area represent the logistic regression model prediction and 95% confidence interval of predictions. Points show exposure of individual subjects with events (P=1) and without events (P=0). Black squares and vertical green lines show observed fraction of subjects with events in each exposure group and 95% confidence interval for these fractions. Dashed vertical lines show bounds of exposure groups. Box plot of exposure is shown by the yellow box with whiskers.
Source: popPK Report Figure 12

Figure 31: Applicant – Logistic Regression for Complete Response: GCT3013-01 and GCT3013-04, Subjects Administered Full Dose of 48 mg



Abbreviations: AUC = area under the concentration-time curve; DLBCL = diffuse large B-cell lymphoma; LBCL = large B-cell lymphoma; n = number of subjects.
Left: LBCL; right: DLBCL. The red solid line and green shaded area represent the logistic regression model prediction and 95% confidence interval of predictions. Points show exposure of individual subjects with events (p=1) and without events (p=0). Black squares and vertical green lines show observed fraction of subjects with events in each exposure group and 95% confidence interval for these fractions. Dashed vertical lines show bounds of exposure groups. Box plot of exposure is shown by the yellow box with whiskers.
Source: popPK Report Figure 13

Figure 32: Applicant – Logistic Regression for Overall Response: GCT3013-01

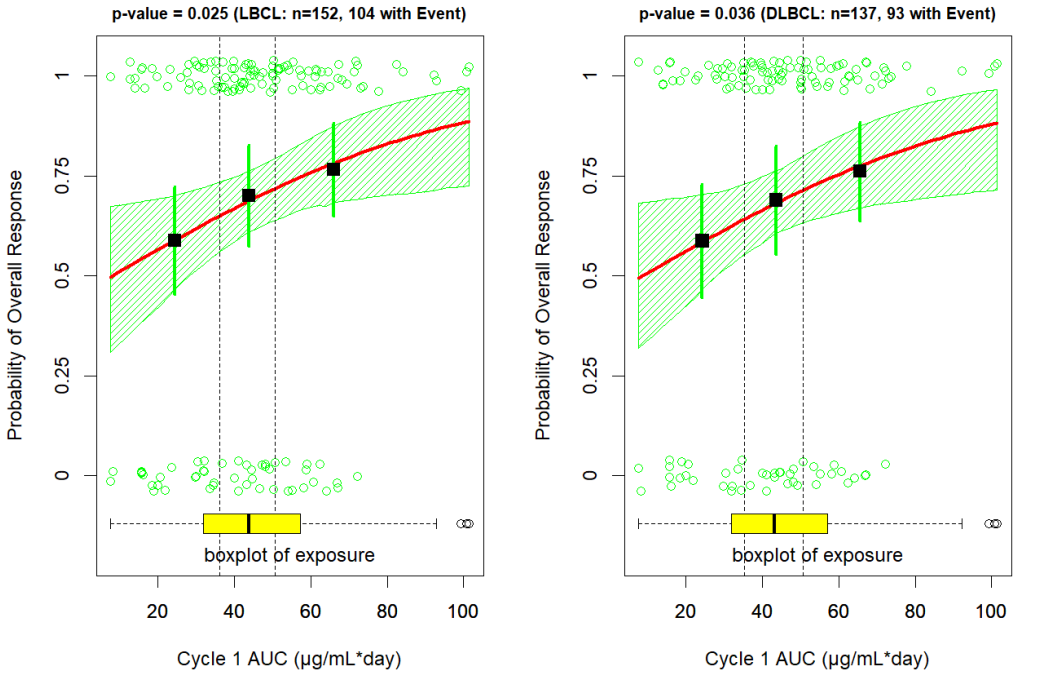


Abbreviations: AUC = area under the concentration-time curve; DLBCL = diffuse large B-cell lymphoma; LBCL = large B-cell lymphoma; n = number of subjects.

Left: LBCL; right: DLBCL. The red solid line and green shaded area represent the logistic regression model prediction and 95% confidence interval of predictions. Points show exposure of individual subjects with events (p=1) and without events (p=0). Black squares and vertical green lines show observed fraction of subjects with events in each exposure group and 95% confidence interval for these fractions. Dashed vertical lines show bounds of exposure groups. Box plot of exposure is shown by the yellow box with whiskers.

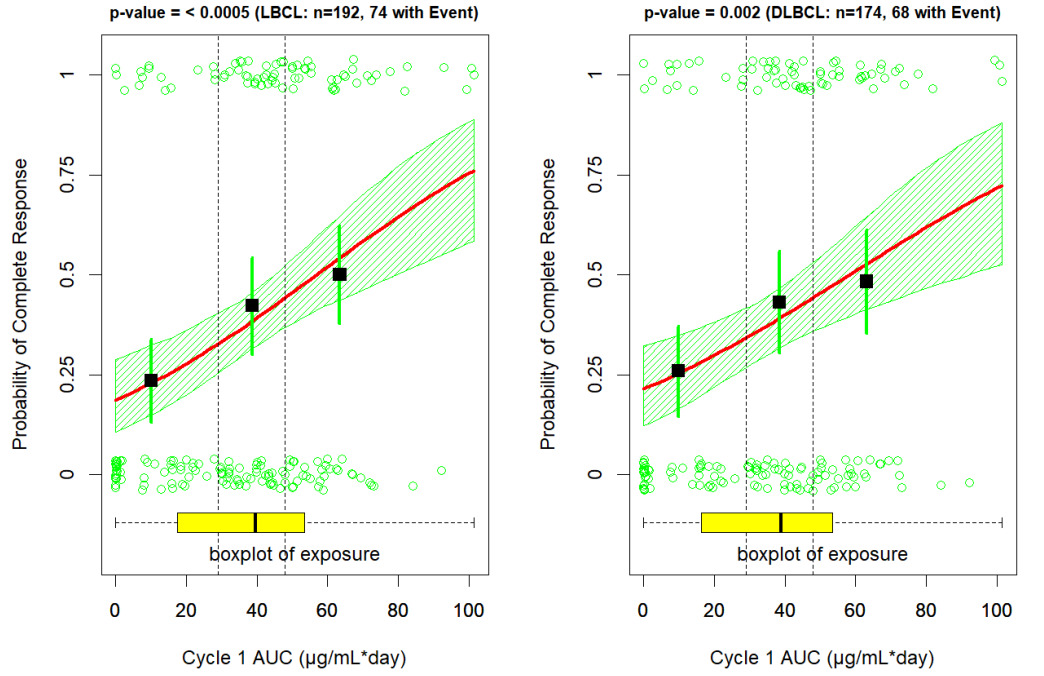
Source: popPK Report Figure 101

Figure 33: Applicant – Logistic Regression for Overall Response: GCT3013-01, Subjects Administered Full Dose of 48 mg



Abbreviations: AUC = area under the concentration-time curve; DLBCL = diffuse large B-cell lymphoma; LBCL = large B-cell lymphoma; n = number of subjects.
Left: LBCL; right: DLBCL. The red solid line and green shaded area represent the logistic regression model prediction and 95% confidence interval of predictions. Points show exposure of individual subjects with events (p=1) and without events (p=0). Black squares and vertical green lines show observed fraction of subjects with events in each exposure group and 95% confidence interval for these fractions. Dashed vertical lines show bounds of exposure groups. Box plot of exposure is shown by the yellow box with whiskers.
Source: popPK Report Figure 102

Figure 34: Applicant – Logistic Regression for Complete Response: GCT3013-01

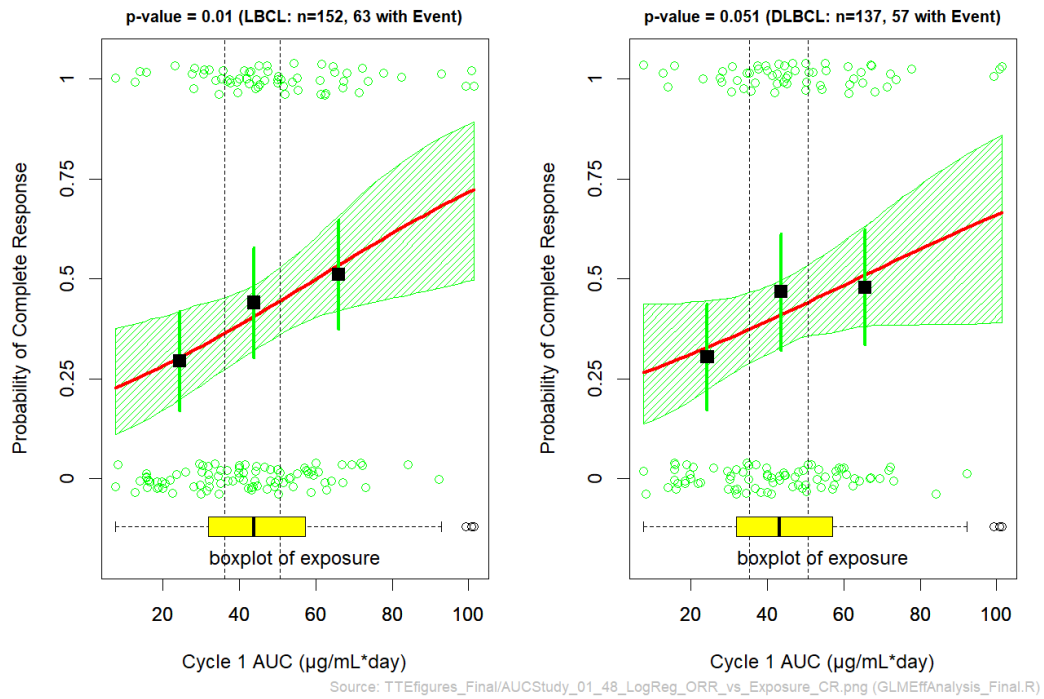


Abbreviations: AUC = area under the concentration-time curve; DLBCL = diffuse large B-cell lymphoma; LBCL = large B-cell lymphoma; n = number of subjects.

Left: LBCL; right: DLBCL. The red solid line and green shaded area represent the logistic regression model prediction and 95% confidence interval of predictions. Points show exposure of individual subjects with events (p=1) and without events (p=0). Black squares and vertical green lines show observed fraction of subjects with events in each exposure group and 95% confidence interval for these fractions. Dashed vertical lines show bounds of exposure groups. Box plot of exposure is shown by the yellow box with whiskers.

Source: popPK Report Figure 103

Figure 35: Applicant – Logistic Regression for Complete Response: GCT3013-01, Subjects Administered Full Dose of 48 mg



Abbreviations: AUC = area under the concentration-time curve; DLBCL = diffuse large B-cell lymphoma; LBCL = large B-cell lymphoma; n = number of subjects.
Left: LBCL; right: DLBCL. The red solid line and green shaded area represent the logistic regression model prediction and 95% confidence interval of predictions. Points show exposure of individual subjects with events (p=1) and without events (p=0). Black squares and vertical green lines show observed fraction of subjects with events in each exposure group and 95% confidence interval for these fractions. Dashed vertical lines show bounds of exposure groups. Box plot of exposure is shown by the yellow box with whiskers.
Source: popPK Report Figure 104

The FDA's Assessment

The E-R efficacy analysis supports the proposed dosage in patients with R/R DLBCL.

Univariate logistic regression found that higher Cycle 1 AUC was associated with better ORR and CR rate (Figure 28 and Figure 30, respectively) in patients with LBCL (n=234) and in patients with DLBCL (n=215) from Study GCT3013-01 and GCT3013-04 who received individual doses ranging from 0.004 to 60 mg SC.

Higher ORR was also associated with higher Cycle 1 C_{trough} using an E_{max} model structure, as shown in Figure 2 in Section 6.2.2.1, which suggests that the Cycle 1 C_{trough} effect on ORR plateaus around the median C_{trough} following the proposed dosage regimen. However, the observed rates of ORR appear to fit the univariate logistic regression models better than the univariate E_{max} model. Due to model uncertainty and lack of robust clinical data at full doses

above 48 mg QW, it is unclear if ORR differs following full doses above 48 mg QW compared to the proposed dosage regimen (0.16/0.8/48 mg).

Multivariate E-R efficacy analysis was conducted in patients with LBCL from Study GCT3013-01 and GCT3013-04 (n=234) for the endpoint of ORR. Higher cycle 1 AUC was associated with better ORR after accounting for the impacts of prior CAR-T therapy status and duration since prior CD20 therapy on ORR (Table 102). Patients with higher Cycle 1 AUC, no prior CAR-T therapy and greater than median duration since prior CD20 therapy at baseline (i.e., greater than 4.8 months since prior CD20 therapy at baseline) tended to have better ORR.

OS and PFS data were available in a total of 237 patients with LBCL from Study GCT3013-01 and GCT3013-04 who received individual doses ranging from 0.004 to 60 mg SC, and the Cycle 1 AUC in these patients is summarized in Table 103. In the E-R efficacy analysis, Cycle 1 AUC was determined using actual dosage records for each patient. If a patient interrupted treatment following the first or the second dose and then restarted treatment, Cycle 1 was defined as 4-week interval following treatment restart.

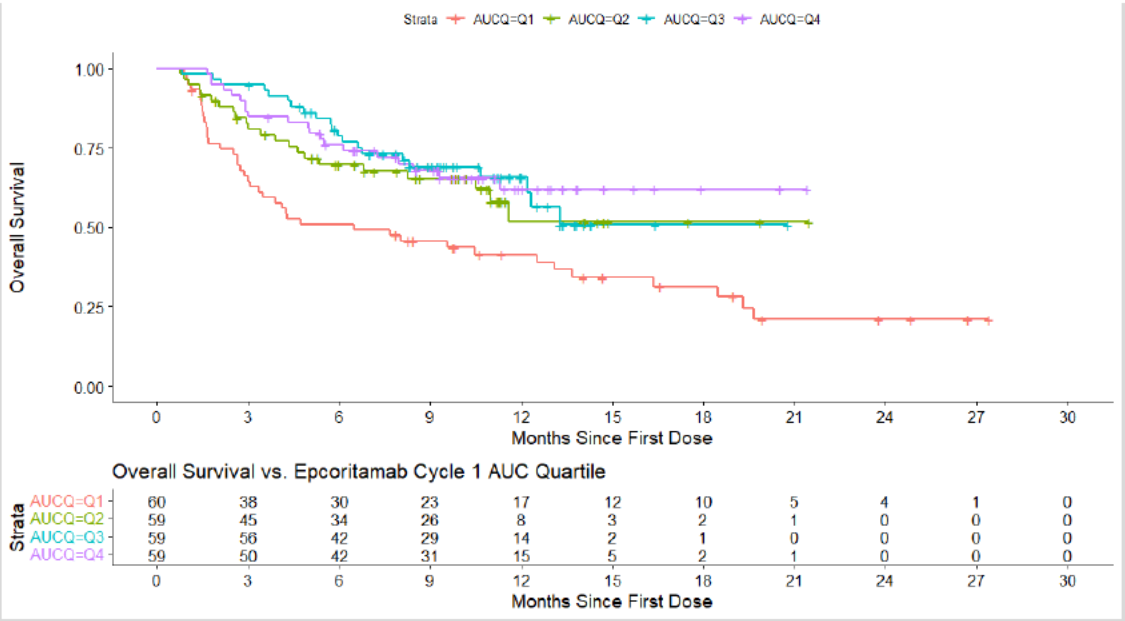
Table 103: Summary of Cycle 1 AUC in Patients with E-R Efficacy Dataset

Exposure metric	Statistic	Quartile 1	Quartile 2	Quartile 3	Quartile 4
Cycle 1 AUC (ug/mL*day)	n	60	59	59	59
	Median	7.65	33.8	48.7	67
	Min – Max	0.00211 - 21.8	21.9 - 41.3	41.6 - 57.1	57.4 - 101.4

Data shown for 237 patients with LBCL in Study GCT3013-01 and GCT3013-04 who received individual epcoritamab doses from 0.004 to 60 mg SC and had recorded exposure, OS, and PFS data.
AUC = area under the concentration-versus-time curve; OS = overall survival; PFS = progression-free survival.
Source: Reviewer's analysis

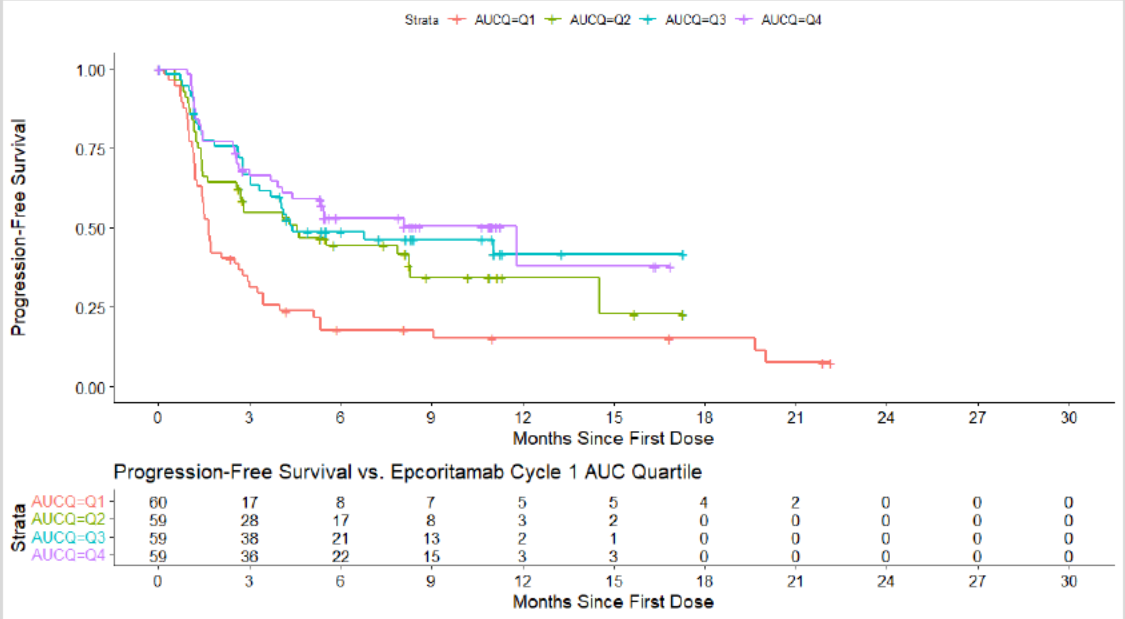
Kaplan-Meier plots show that the lowest Cycle 1 AUC quartile was associated with worse OS (Figure 36) and worse PFS (Figure 37) compared to higher exposure quartiles.

Figure 36: Kaplan-Meier Plot of Overall Survival by Cycle 1 AUC Quartile



Data shown for 237 patients with LBCL from Study GCT3013-01 and GCT3013-04 who received individual epcoritamab doses ranging from 0.004 to 60 mg SC. AUC = area under the concentration-versus-time curve; AUCQ = Cycle 1 AUC quartile; Q = quartile; Q1 = 1st quartile (i.e., lowest exposure quartile).
Source: Reviewer's analysis

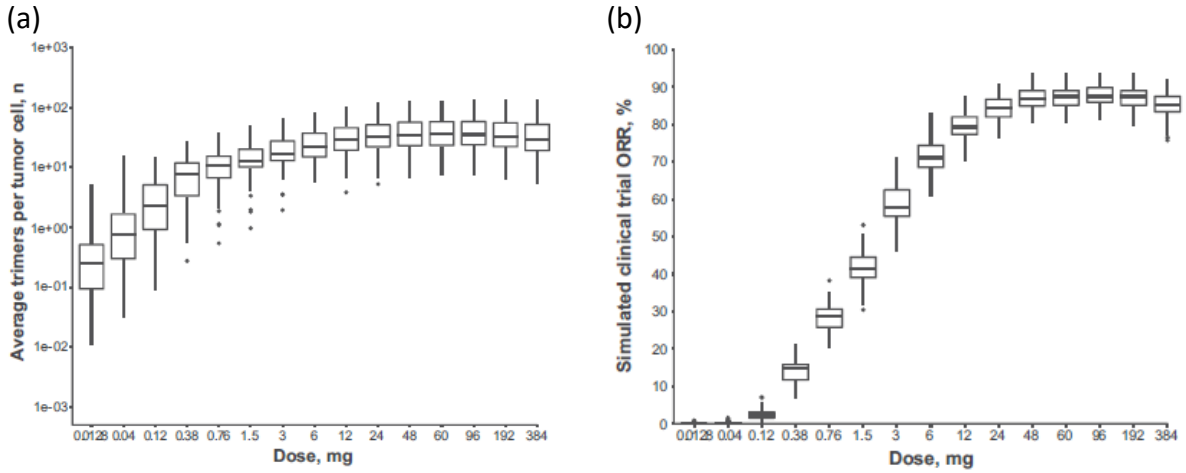
Figure 37: Kaplan-Meier Plot of Progression-Free Survival by Cycle 1 AUC Quartile



Data shown for 237 patients with LBCL from Study GCT3013-01 and GCT3013-04 who received individual epcoritamab doses ranging from 0.004 to 60 mg SC. AUC = area under the concentration-versus-time curve; AUCQ = Cycle 1 AUC quartile; Q = quartile; Q1 = 1st quartile (i.e., lowest exposure quartile).
Source: Reviewer's analysis

Besides the above-mentioned E-R analysis, the Applicant also conducted PK/PD analysis to inform epcoritamab dose selection for patients with B-cell Lymphomas (Hutchings et al, 2021; Li et al. 2022), where a semi-mechanistic physiologically-based pharmacokinetic/ pharmacodynamic (PBPK/PD) model was developed to quantitatively describe biodistribution, trimer formation (i.e., target engagement and crosslinking of epcoritamab to both CD3 and CD20), and tumor response using preclinical, clinical PK, biomarker, tumor, and response data from the dose-escalation part of study GCT3013-01. Using formation of trimer as the driving force, this semi-mechanistic PBPK/PD model predicted clinical response rate started to plateau at 48 mg and started to decrease at doses higher than 192 mg (Figure 38).

Figure 38: Semi-mechanistic PBPK/PD Model-predicted trimer formations (a) simulated clinical trial ORRs (b) in patients with DLBCL.



Source: Li et al. 2022.

Although this modeling analysis was not included in the BLA submission, the FDA considered that the modeling results appeared generally reasonable from a mechanism of action perspective, and may be used to support the selection of epcoritamab 48 mg full dose in the intended patient population.

References:

Hutchings M, et al. Dose escalation of subcutaneous epcoritamab in patients with relapsed or refractory B-cell non-Hodgkin lymphoma: an open-label, phase 1/2 study. Lancet. 2021 Sep 25;398(10306):1157-1169.

Li T, et al. Semi-mechanistic Physiologically-Based Pharmacokinetic/Pharmacodynamic Model Informing Epcoritamab Dose Selection for Patients With B-Cell Lymphomas. Clin Pharmacol Ther. 2022 Nov;112(5):1108-1119.

19.4.5.3. ER (safety) Executive Summary

The FDA's Assessment:

The E-R safety analysis did not identify any safety issues with the proposed epcoritamab dosage regimen. Patients with higher exposure were more likely to experience injection site reactions, but no other E-R safety associations with higher Cycle 1 AUC were identified.

19.4.5.4. ER (safety) Assessment Summary

The Applicant's Position:

General Information	
Goal of ER analysis	The objectives of the exposure-safety analysis were to assess the relationships between epcoritamab exposures and key safety endpoints
Study Included	GCT3013-01 and GCT3013-04
Population Included	Relapsed, Progressive or Refractory B-Cell Lymphoma, including aNHL, iNHL, and MCL
Endpoint	CRS, (any grade, grade ≥2, CRS requiring tocilizumab); ICANS (any grade); CTLS (any grade); grade ≥3 treatment-emergent adverse events (TEAE); serious TEAE; TEAE leading to dose delay; TEAE leading to treatment discontinuation; grade ≥3 Neutropenia (TEAE); grade ≥3 Infections (TEAE); injection site reactions.
No. of Patients (total, and with individual PK)	359 patients
Dose(s) Included	Priming doses of epcoritamab tested include 0.004, 0.0128, 0.04, 0.08, 0.12, and 0.16 mg. Intermediate doses of epcoritamab tested include 0.25, 0.5, 0.8, and 1.6 mg. Full doses of epcoritamab tested include 0.0128, 0.04, 0.12, 0.38, 0.76, 1.5, 3, 6, 12, 24, 48, and 60 mg
Exposure Metrics Explored (range)	Predicted AUC over the first cycle (Cycle 1 AUC); Predicted C_{max} following each of the 4 doses of Cycle 1.
Covariates Evaluated	N/A

Final Model Parameters	Summary	Acceptability [FDA's comments]
Model Structure	Linear logistic regression model	Logistic regression and comparison of TEAE rates across Cycle 1 AUC tertiles was conducted. The E-R safety analysis was limited by use of Cycle 1 AUC following actual dosing records as the exposure metric because associations were
Model Parameter Estimates	N/A	
Model Evaluation	N/A	
Covariates and Clinical Relevance	N/A	
Simulation for Specific Population	N/A	

Final Model Parameters	Summary	Acceptability [FDA's comments]
		confounded by patients with dose modification due to TEAE prior to the last dose of Cycle 1. The impact of confounding resulted in the highest rates of multiple TEAEs in the lowest exposure tertile.
Visualization of E-R relationships	A tabular presentation of AEs by exposure tertiles is provided in Table 23 and Table 104. The results of the logistic regression analysis to evaluate the relationship between epcoritamab exposures and AEs was evaluated in exposure-safety analyses. These figures are available in the PopPK report Figure 69 to 100.	The incidence of anemia, neutropenia, and thrombocytopenia derived from the laboratory dataset is summarized according to Cycle 1 AUC tertile in Table 105. Higher Cycle 1 AUC was associated with a higher incidence of injection site reactions (Figure 39).
Overall Clinical Relevance for ER	Across the dose range studied (0.004 to 60 mg), no increase in incidence of any TEAE category tested was seen with increasing epcoritamab exposure. Increased epcoritamab exposure did not result in increased ≥grade 3 TEAEs (including neutropenia and infections) or serious TEAEs. Importantly, increased epcoritamab exposure did not result in higher incidence of any grade CRS, ≥grade 2 CRS, CRS requiring tocilizumab, ICANS, and CTLS across the doses and exposures evaluated. In addition, the relative dose intensity remained approximately 95% or higher regardless of PK exposure to epcoritamab or of dosing period (Cycles 1 to 3, Cycles 4 to 9, and Cycle 10+).	Although the E-R analysis was limited by confounding from early dose modifications, the E-R safety analysis did not identify any safety risks and generally supports the proposed dosage regimen.
Labeling Language	**Description**	**Acceptability [FDA's comments]**
12.2 Pharmacodynamics	PopPK Report Figure 20 and 21 and Figure 145 – 149	No E-R safety statements are included in the labeling

Table 104: Applicant – Frequencies of Adverse Events, by Exposure Tertiles: All Data (GCT3013-01 + GCT3013-04; Escalation + Expansion; PK Evaluable Subjects at All Dose Levels in Escalation Part)

	R/R LBCL (N=237) n (%)			R/R DLBCL (N=217) n (%)			All B-NHL (N=359) n (%)		
Exposure (Cycle 1 AUC) Tertile (N)	**Tertile 1 N=79**	**Tertile 2 N=79**	**Tertile 3 N=79**	**Tertile 1 N=72**	**Tertile 2 N=72**	**Tertile 3 N=73**	**Tertile 1 N=120**	**Tertile 2 N=119**	**Tertile 3 N=120**
Exposure range (µg/mL*day)	0.0021; 30.7	30.9 ; 50.3	50.4 ; 101	0.0021;31.4	31.6 ; 50.4	50.6 ; 101	0.0021;27.8	27.9 ; 47.3	47.5 ; 101
AE type									
Grade ≥3 TEAE	58 (73.4%)	50 (63.3%)	54 (68.4%)	51 (70.8%)	46 (63.9%)	51 (69.9%)	93 (77.5%)	71 (59.7%)	84 (70%)
Serious TEAE	52 (65.8%)	35 (44.3%)	41 (51.9%)	48 (66.7%)	31 (43.1%)	38 (52.1%)	86 (71.7%)	58 (48.7%)	63 (52.5%)
Grade ≥3 neutropenia (TEAE)	19 (24.1%)	22 (27.8%)	23 (29.1%)	16 (22.2%)	20 (27.8%)	22 (30.1%)	32 (26.7%)	28 (23.5%)	32 (26.7%)
Grade ≥3 infections (TEAE)	19 (24.1%)	8 (10.1%)	15 (19%)	16 (22.2%)	8 (11.1%)	13 (17.8%)	33 (27.5%)	14 (11.8%)	23 (19.2%)
Injection site reactions	29 (36.7%)	28 (35.4%)	39 (49.4%)	26 (36.1%)	27 (37.5%)	38 (52.1%)	50 (41.7%)	45 (37.8%)	63 (52.5%)
TEAE leading to treatment discontinuation	14 (17.7%)	3 (3.8%)	3 (3.8%)	13 (18.1%)	3 (4.2%)	3 (4.1%)	14 (11.7%)	6 (5%)	4 (3.3%)
TEAE leading to dose delay/interruption	27 (34.2%)	32 (40.5%)	25 (31.6%)	24 (33.3%)	28 (38.9%)	24 (32.9%)	56 (46.7%)	48 (40.3%)	44 (36.7%)
CRS (all grade)	50 (63.3%)	36 (45.6%)	55 (69.6%)	45 (62.5%)	33 (45.8%)	51 (69.9%)	84 (70%)	64 (53.8%)	77 (64.2%)
Grade 2 or above	23 (29.1%)	17 (21.5%)	17 (21.5%)	19 (26.4%)	15 (20.8%)	17 (23.3%)	48 (40%)	18 (15.1%)	25 (20.8%)
Tocilizumab required	21 (26.6%)	10 (12.7%)	13 (16.5%)	18 (25%)	9 (12.5%)	13 (17.8%)	38 (31.7%)	17 (14.3%)	18 (15%)
ICANS (all grade)	2 (5.3%)	2 (2.7%)	4 (5.3%)	2 (5.7%)	1 (1.5%)	4 (5.8%)	4 (6.2%)	4 (3.5%)	5 (4.4%)
CTLS (all grade)	3 (3.8%)	0 (0%)	0 (0%)	1 (1.4%)	0 (0%)	0 (0%)	4 (3.3%)	0 (0%)	0 (0%)
Relative dose intensity									
Overall (dose escalation part)	99.9 (0.5)	100 (0)	100 (0.1)	99.9 (0.6)	100 (0)	100 (0.1)	98.8 (7.2)	100 (0)	100 (0.1)
Cycle 1-3 (expansion part)	94.2 (11.6)	97.4 (5.8)	96.1 (8.2)	95.4 (10.8)	97.6 (5.8)	96.1 (8.1)	92.7 (12.6)	96 (7.5)	95.6 (8.4)
Cycle 4-9 (expansion part)	98.8 (2.7)	98.2 (4.2)	99 (2.9)	98.6 (2.7)	98.1 (4.4)	98.9 (3.1)	96.2 (11.4)	98 (5.1)	98.3 (4.3)
Cycle 10+ (expansion part)	99.5 (1.4)	98.7 (4.2)	99.2 (3.4)	99.6 (1.3)	98.7 (4.3)	99.1 (3.5)	98.5 (3.9)	98.8 (3.9)	99.5 (3)

Abbreviations: AE = adverse event; AUC = area under the concentration-time curve; CRS = cytokine release syndrome; CTLS = clinical tumor lysis syndrome; DLBCL = diffuse large B-cell lymphoma; ICANS = immune effector cell-associated neurotoxicity syndrome; LBCL = large B-cell lymphoma; N = number of subjects; PK = pharmacokinetics; R/R = relapsed or refractory; TEAE = treatment-emergent adverse events.

Missing values were removed from summaries.

Source: Safety_Tables_1_3_Final.csv, DoseIntensity_Tables_1_3_Final.csv (PrepareDataSafety_Final.R)

The FDA's Assessment:

The E-R safety analysis did not identify any safety issues with the proposed epcoritamab dosage regimen.

Table 104 summarizes rates of select TEAEs according to tertile of Cycle 1 AUC. The highest Cycle 1 AUC tertile was associated with the highest rate of injection site reactions overall and in the subgroup of patients with LBCL.

No clear trends were identified for the other selected TEAEs in Table 104, although the associations across Cycle 1 AUC tertiles may have been confounded by patients who discontinued treatment due to TEAE prior to the last dose in Cycle 1. In the E-R safety analysis, Cycle 1 AUC was determined using actual dosage records for each patient. If a patient interrupted treatment following the first or the second dose and then restarted treatment, Cycle 1 was defined as the 4-week interval following treatment restart. The use of actual dosing records to calculate Cycle 1 AUC may explain why the lowest exposure tertile has the highest incidence of multiple TEAEs in Table 104Table 104, such as TEAE leading to discontinuation, CRS requiring tocilizumab administration, and clinical tumor lysis syndrome (CTLS).

The rates of neutropenia in Table 104 are derived from the adverse event dataset (ADAE.xpt) which may have lower recorded rates of cytopenias and other adverse events defined by lab values compared to the laboratory dataset (ADLB.xpt). Rates of anemia, neutropenia, and thrombocytopenia derived from the laboratory dataset are summarized for each Cycle 1 AUC tertile in Table 105.

Higher Cycle 1 AUC had no clear associations with anemia, neutropenia, or thrombocytopenia. The lowest Cycle 1 AUC tertile had the highest rate of any grade and Grade ≥3 thrombocytopenia derived from the laboratory dataset, which may be related to use of Cycle 1 AUC from actual dosing records as the exposure metric and patients who discontinued treatment prior to the last dose in Cycle 1.

Table 105: Cycle 1 AUC Quartile Versus Rates of Anemia, Neutropenia, and Thrombocytopenia Derived from the Laboratory Dataset

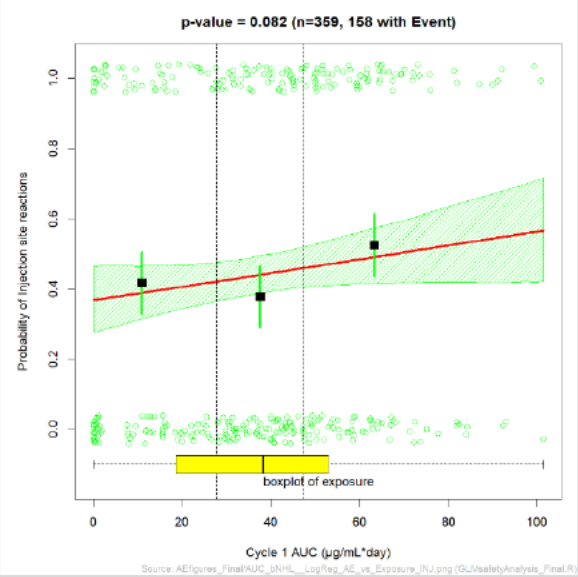
		GCT3013-01 and GCT3013-04 R/R LBCL			
	Statistic	Cycle 1 AUC Tertile 1 N=79	Cycle 1 AUC Tertile 2 N=79	Cycle 1 AUC Tertile 3 N=79	Overall (N=237)
Cycle 1 AUC (µg/mL*day)	Min, Max	0.0021, 30.7	30.9, 50.3	50.4, 101	0.0021, 101
Anemia any grade	n (%) [95% CI]	50 (63.3) [52.7-73.9]	48 (60.8) [50-71.5]	50 (63.3) [52.7-73.9]	148 (62.4) [56.3-68.6]
Anemia grade ≥3	n (%) [95% CI]	15 (19) [10.3-27.6]	12 (15.2) [7.3-23.1]	8 (10.1) [3.5-16.8]	35 (14.8) [10.3-19.3]
Neutropenia any grade	n (%) [95% CI]	31 (39.2) [28.5-50]	32 (40.5) [29.7-51.3]	27 (34.2) [23.7-44.6]	90 (38) [31.8-44.2]

		GCT3013-01 and GCT3013-04 R/R LBCL			
	Statistic	Cycle 1 AUC Tertile 1 N=79	Cycle 1 AUC Tertile 2 N=79	Cycle 1 AUC Tertile 3 N=79	Overall (N=237)
Neutropenia grade ≥3	n (%) [95% CI]	20 (25.3) [15.7-34.9]	19 (24.1) [14.6-33.5]	18 (22.8) [13.5-32]	57 (24.1) [18.6-29.5]
Thrombocytopenia any grade	n (%) [95% CI]	48 (60.8) [50-71.5]	38 (48.1) [37.1-59.1]	41 (51.9) [40.9-62.9]	127 (53.6) [47.2-59.9]
Thrombocytopenia grade ≥3	n (%) [95% CI]	16 (20.3) [11.4-29.1]	12 (15.2) [7.3-23.1]	7 (8.9) [2.6-15.1]	35 (14.8) [10.3-19.3]

AE = adverse event; AUC = area under the concentration-versus-time curve; CI = confidence interval.
Data cutoff date: 31 Jan 2022
Source: Table 3 in Applicant's 2 December 2022 response to 22 November 2022 information request

In Study GCT3013-01 and GCT3013-04 patients with B-NHL (n=359), logistic regression suggested that higher Cycle 1 AUC may be associated with higher incidence of injection site reactions, as shown in Figure 39. The lowest Cycle 1 AUC tertile has slightly higher incidence of injection site reaction compared to the middle tertile, which may be due to confounding from patients who discontinued treatment prior to the last dose of Cycle 1.

Figure 39: Logistic Regression for Injection Site Reactions: All Patients



The red solid line and green shaded area represent the logistic regression model prediction and 95% confidence interval of predictions. Points show exposure of individual subjects with events (p=1) and without events (p=0). Black squares and vertical green lines show observed fraction of subjects with events in each exposure group and 95% confidence interval for these fractions. Dashed vertical lines show bounds of exposure groups. Box plot of exposure is shown by the yellow box with whiskers. AUC = area under the concentration-time curve; n = number of subjects.
Source: Figure 78 in Applicant's PPK/E-R Report

Logistic regression did not identify any associations between higher Cycle 1 AUC and incidence of any grade CRS, grade ≥2 CRS, CRS treated with tocilizumab administration, serious AE, Grade ≥3 TEAE, Grade ≥3 neutropenia derived from AE dataset, Grade ≥3 infections, AE leading to dose delay, or AE leading to discontinuation. Logistic regression also did not identify any E-R safety associations with CTLS or ICANS although the analysis may have been limited by the relatively low numbers of these safety events.

19.4.5.5. Overall benefit-risk evaluation based on E-R analyses

The Applicant's Position:

Overall, the exposure-safety analyses suggest that the proposed 0.16 mg priming dose and 0.8 mg intermediate dose of epcoritamab produced similar or lower peak IL-6 concentrations and Grade 2 or higher CRS incidence compared with the other priming and intermediate doses tested. No increase in incidence of any TEAE category tested was seen with increasing epcoritamab exposure. In addition, the relative dose intensity remained approximately 95% or higher regardless of PK exposure or of dosing period. Based on the exposure -efficacy analyses, across the full dose range of 0.004 to 60 mg studied, statistically significant ($P<0.05$) relationships between key efficacy endpoints (ORR, CR rate, PFS, and OS) and epcoritamab exposure were observed, ie, higher epcoritamab exposures provided higher ORR/CR rate and longer PFS/OS. A similar, numerical trend was also observed for DOR.

At the proposed 48 mg full dose (ie, analysis using data only from 48 mg full dose level), exposure-efficacy relationships remained positive for all the key efficacy endpoints and were statistically significant ($P<0.05$) for CR rate. These results indicate that full doses <48 mg are likely to result in compromised efficacy.

TMDD saturation was observed starting from 48 mg, due to a plateau in tumor killing. In addition, less significant exposure-efficacy relationships were observed when data from the 48 mg dose alone were analyzed when compared to data from across all doses. The exposure-efficacy relationships for ORR, PFS, and OS are no longer statistically significant using 48 mg data alone. Therefore, full doses >48 mg are not expected to lead to significantly higher efficacy.

Based upon these results, the proposed priming (0.16 mg) and intermediate (0.8 mg) doses of epcoritamab represents a step-up dosing regimen that mitigates the incidence of ≥grade 2 CRS, in subjects with R/R LBCL (including DLBCL). In addition, the proposed full dose (48 mg) of epcoritamab is appropriate in the LBCL patient population, providing significantly better efficacy with a manageable safety profile when compared to lower doses. Decreasing the full dose of epcoritamab is likely to result in compromised efficacy, without improvement of the benefit-risk profile, in subjects with R/R LBCL and the 48 mg dose reasonably balances benefit-risk in this population. Furthermore, increasing the full dose >48 mg is not expected to lead to significantly higher efficacy. No dose adjustment is needed for specific populations.

The FDA's Assessment:
The E-R efficacy and safety analyses generally support the proposed dosage regimen. Exposure following the proposed full dose of 48 mg QW was not associated with any major safety concerns. Full doses below 48 mg QW would likely result in worse efficacy outcomes compared to the proposed 48 mg QW full dose. Based on current data, it is not clear if clinical efficacy outcomes would differ between the proposed 48 mg QW full dose and full doses above 48 mg QW.

19.4.6. Immunogenicity

BLA number:	BLA 761324 / Original submission
Product name:	Epcoritamab (GEN3013)
Reviewers:	Mohsen Rajabi and Yow-Ming Wang (Therapeutic Biologics Program, OCP) Ider Peter Lee (Knowledge Management Team, OCP)

1. Summary of clinical studies

Immunogenicity of epcoritamab was evaluated in a pivotal phase 1/2 study GCT3013-01. Table 106 contains (1) the information for this study assessing immunogenicity and (2) a high-level summary of study results for PK (trough concentration). Overall study design in terms of treatment duration, sampling time and size, demographics was adequate to assess the ADA impact on PK.

Table 106: Summary of clinical study information and immunogenicity incidence

	Clinical study information
Study number	GCT3013-01 (Phase 1/2) Dose expansion cohort
Dose regimen	Cycle 1: initial priming at 0.16 mg (C1D1), followed by 0.8 mg (C1D8), and a full dose of 48 mg at C1D15, C1D22, Cycles 2-3: 48 mg QW Cycles 4-9: 48 mg Q2W Cycle 10 & beyond: 48mg Q4W Note: Each cycle is 4 weeks.
Route of administration	SC
Treatment duration	administered until disease progression or unacceptable toxicity
Status	Ongoing
Number patients that received epcoritamab	157 patients with large B-cell lymphoma (LBCL) in the aNHL cohort

	Clinical study information
Study number	GCT3013-01 (Phase 1/2) Dose expansion cohort
Applicant reported ADA incidence	4/158 (2.5 %)
Applicant reported NAb incidence	Not assessed
FDA calculated ADA incidence	4/156 (2.6%)
FDA calculated Nab incidence (among ADA+)	Not assessed
Applicant reported epcoritamab trough concentration data (µg/mL)	Geometric Mean (CV%) C1D8: 5.1 (19.88%) n=134, C1D15: 9.3 (84.79%) n=137, C1D22: 1739.4 (92.98%) n=128 C4D15: 6236.7 (60.50%) n=76 C11D1: 2635.7 (41.98%) n=8
Data Source, CSR number	GCT3013-01 expansion cohort

2. Highlight of key characteristics of immunogenicity assays relevant to this review

The ADA assay has adequate sensitivity and drug tolerance. Table 107 shows several assay characteristics that are relevant for the analysis evaluating the impact of ADA on PK.

Table 107: Summary of key assay characteristics related to immunogenicity assessment

Study	GCT3013-01 (Phase 1/2)
Assay validation report number (ADA and NAb)	PRA-NL-LML-2108
ADA assay sensitivity	The assay sensitivity was 100 ng/mL.
ADA assay drug tolerance	50 ug/mL of drug in the presence of 100 ng/mL PC
Sources	Table 13 of validation report PRA-NL-LML-2108

3. Methods for evaluating the effect of immunogenicity on PK of epcoritamab

To evaluate the impact of immunogenicity on PK, we compared the observed concentrations in two groups (ADA+ and ADA-) in patients with time-matched PK and ADA data using

Immunogenicity Specimen (IS) tool developed in-house. At each timepoint epcoritamab concentrations by ADA status (ADA+ or ADA-) were tabulated by timepoint, including the number of patients, the geometric mean ratio (GMR) of ADA+/ADA- and the corresponding 90% CI.

Data from GCT3013-01 expansion cohort (LBCL indication) were analyzed and summarized below.

4. Effect of immunogenicity on PK of epcoritamab – Results

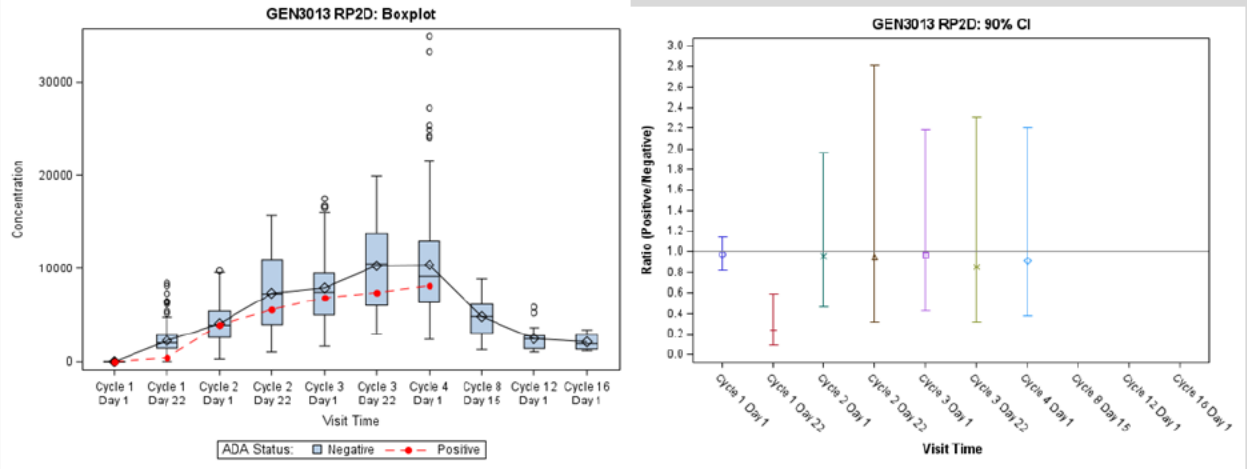
The results indicate that the impact of ADA occurred early in the treatment and drug concentration was lower for ADA + patient.

Study GCT3013-01

Figure 40 and Table 108 contain epcoritamab concentration data for patients with matched PK and ADA samples and the GMR (90% CI) comparing ADA+ group to ADA- group.

At C1D22, ADA+ group (n=4) had a lower epcoritamab concentration than ADA- group (n=127) at C1D22 indicating that ADA had a negative effect on PK of epcoritamab. From cycle 2 onwards, there were only 1-2 ADA + patients, as such there is insufficient data to evaluate the impact of ADA on PK. Among 4 timepoints with one single ADA+ patient, C4D1 had a GMR of 0.4 whereas the GMR for other timepoints were close to the value of 1; all 90%CI included the value of 1. For the purpose of a qualitative assessment of the GMR trend over time, Table 108 included the GMR and 90%CI were estimated for 4 timepoints with a single ADA+ patients.

Figure 40: Left Panel: Box plot analysis of drug concentration from ADA positive and ADA negative samples during the treatment period (17 cycle). Right Panel: 90% confidence interval of GMR of drug concentration at each visit.



RP2D = dose regimen described in Table 1.

Table 108. Study GCT3013-01 - Summary of average epcoritamab concentration by ADA status at each study visit and the geometric mean ratio of ADA+ to ADA-.

Visit #	Treatment week	Total N	Epcoritamab Concentration (µg/mL), geometric mean				GMR (90%CI) ADA+/ADA-
			ADA+ group	N	ADA- group	N	
C1D1	1	144	5.0	4	5.46	140	0.97 (0.83,1.14)
C1D22	4	131	415.32	4	1759.97	127	0.23 (0.09,0.58)
C2D1	5	119	3344.96	2	3478.61	115	0.96 (0.47,1.96)
C2D22	8	29	5563.45	1	5874.41	28	0.94 (0.31,2.8) *
C3D1	9	100	6859.82	1	7085.95	99	0.85 (0.31,2.3) *
C3D22	12	19	7400.26	1	8658.19	18	0.91 (0.37, 2.2) *
C4D1	13	83	8150.36	1	8971.67	82	0.4 (0.2,0.9) *
C8D15	33	30	-	0	4379.13	30	-
C12D1	49	12	-	0	2256.65	12	-
C16D1	65	2	-	0	1917.98	2	-

N: number of patients; GMR: geometric mean ratio; CI: confidence interval; concentration data reported to 2 decimal places.
* 90%CI was estimated based on data from a single ADA+ patient for qualitative evaluations of the GMR trend.

19.5. FDA Grouped Preferred Terms

The FDA's Assessment:

The FDA used the following grouped preferred terms in the reivew of safety for this application.

Table 109: FDA Table of Grouped Preferred Terms

FDA Grouped PT	Included	Not Included
Abdominal pain	abdominal discomfort, abdominal pain abdominal pain lower, abdominal pain upper, abdominal tenderness	Abdominal distension, dyspepsia, GERD
Administration related Reaction	Infusion related reaction, injection site reaction, injection site erythema/hypertrophy/inflammation/edema /mass/pain/pruritus/rash/swelling/urticaria	Injection site bruising
Anemia	Anemia	iron deficiency anemia
Arthritis or Arthralgia	Arthralgia, arthritis, osteoarthritis	

FDA Grouped PT	Included	Not Included
Atrial fibrillation or flutter	Atrial fibrillation, atrial flutter	
Bruising	Contusion, injection site bruising	Purpura
Cardiac arrhythmias	Bradycardia, sinus bradycardia, sinus tachycardia, supraventricular extrasystoles, supraventricular tachycardia, tachycardia, electrocardiogram Q prolonged, Electrocardiogram T wave abnormal, long QT syndrome, sinus node dysfunction	
Cardiac failure	Cardiac failure, diastolic dysfunction	
Chest pain	Angina pectoris, chest discomfort, chest pain	
Chills	Chills	
Colitis	Enterocolitis infectious	Enteritis, Cytomegalovirus enterocolitis
Constipation	Constipation	
Cough	Cough, productive cough	Upper-airway cough syndrome, habit cough
COVID-19	COVID-19, Asymptomatic COVID-19, COVID-19 pneumonia, SARS-CoV-2 test positive	
Cytokine Release Syndrome	Per Applicant's Grouping	
Cytomegalovirus infection	All PTs containing "Cytomegalovirus": cytomegalovirus chorioretinitis, cytomegalovirus enterocolitis, cytomegalovirus infection, cytomegalovirus infection reactivation, cytomegalovirus viraemia	
Diarrhea	Diarrhea	Irritable bowel syndrome, Diarrhea hemorrhagic
Dizziness	Dizziness, dizziness postural, vertigo	
Dyspnea	Dyspnea, dyspnea exertional	

FDA Grouped PT	Included	Not Included
Edema	Edema, generalized edema, facial edema, edema peripheral, peripheral swelling, pulmonary congestion, swelling face	Localized edema, lymphedema, scrotal edema, swelling of eyelid
Eye Hemorrhage	conjunctival hemorrhage, eye hemorrhage, vitreous hemorrhage	
Fatigue	Asthenia, Fatigue, Lethargy, hypersomnia, somnalence	
Febrile neutropenia	Febrile neutropenia	
Fever	Pyrexia	Tumor associated fever
Fracture	Femoral neck fracture, forearm fracture, hip fracture, osteoporotic fracture, rib fracture, spinal compression fracture, spinal fracture, tooth fracture, wrist fracture	
Gastroenteritis	Gastroenteritis, gastroenteritis viral, campylobacter gastroenteritis, enteritis, food poisoning	Gastritis
Gastrointestinal hemorrhage	Gastrointestinal hemorrhage, small intestinal hemorrhage, anal hemorrhage, upper gastrointestinal hemorrhage, hematochezia, Diarrhea hemorrhagic	
Headache	Headache	
Hematoma	Hematoma, intra-abdominal hematoma	Subdural hematoma
Hemorrhage	All AEDECOD terms contained in FDA's "Gastrointestinal hemorrhage," "Eye hemorrhage," and "hemorrhage intracranial" groupings, retroperitoneal hemorrhage, hematuria, hemoptysis, post-procedural hemorrhage	Lip hemorrhage, mouth hemorrhage
Hemorrhage intracranial	Subdural hematoma, Subarachnoid hemorrhage	
Hepatitis	Liver injury, hepatotoxicity	FDA's "Transaminase elevation" grouping
Herpesvirus infection	Herpes simplex, Herpes simplex reactivation, herpes virus infection, herpes zoster, oral herpes, varicella zoster virus infection	
Hyperbilirubinemia	Blood bilirubin increased	

FDA Grouped PT	Included	Not Included
Hypertension	Hypertension	
Hypogammaglobulinemia	Blood immunoglobulin G decreased, Hypogammaglobulinemia, immunoglobulins decreased	
Hypotension	Hypotension, Orthostatic hypotension	
ICANS	Per Applicant's grouping	
Infusion Related Reactions	Per Applicant's grouping	
Leukocytosis	White blood cell count increase	
Leukopenia	Leukopenia, white blood cell count decrease	
Lower respiratory tract infection	Bronchitis, bronchitis pneumococcal, infective exacerbation of bronchiectasis, lower respiratory tract infection	FDA grouping for pneumonia
Lymphopenia	Lymphocyte count decreased, lymphopenia	
Mucositis	Mucosal inflammation, oral pain, mouth ulceration, oropharyngeal pain, aphthous ulcer, odynophagia, stomatitis, tongue ulceration	Angular cheilitis, gingivitis, esophageal pain, throat irritation
Musculoskeletal pain	Axillary pain, back pain, bone pain, flank pain, musculoskeletal chest pain, musculoskeletal pain, myalgia, neck pain, non-cardiac chest pain, pain, pain in extremity, sacral pain, spinal pain	Groin pain, muscle spasms, musculoskeletal stiffness
Myocardial ischemia or infarction	Acute myocardial infarction, troponin increased	Angina pectoris
Nausea	Nausea	
Neurological changes	Confusional state, delirium, depressed level of consciousness, hallucination, loss of consciousness, memory impairment, mental status changes, tremor, aphasia, ataxia, dysgraphia, deafness, dysphonia,	PTs under FDA's "Vision changes", speech disorder
Neutropenia	Neutropenia, Neutrophil count decreased	Febrile neutropenia
Nonmelanoma skin cancer	Squamous cell carcinoma, Basal cell carcinoma	
Palpitations	Palpitations	

FDA Grouped PT	Included	Not Included
Peripheral neuropathy and paresthesia	Bell's palsy, Hypoesthesia, neuropathy peripheral, paresthesia, facial paralysis, peripheral sensory neuropathy, neuralgia	Eye paresthesia, hypoesthesia oral, acute polyneuropathy, post-herpetic neuralgia, tinnitus
Petechiae and purpura	purpura	
Pneumonia	Bronchopneumopathy, bronchopulmonary aspergillosis, lung infiltration, pneumocystis jirovecii pneumonia, pneumonia, pneumonia aspiration, pneumonia bacterial, pneumonia pneumococcal, empyema, infectious pleural effusion * Cases of COVID-19 pneumonia will be grouped as both pneumonia and as COVID-19	Lung opacity, pleural effusion
Pneumonitis	Pneumonitis, Interstitial lung disease	
Pruritis	Eye pruritus, pruritis	rash pruritic; post-procedural pruritus
Rash	dermatitis acneiform, dermatitis bullous, dermatitis contact, dermatitis exfoliative generalized, drug eruption, erythema, erythema multiforme, exfoliative rash, palmar erythema, penile erythema, rash, rash erythematous, rash maculo-papular, rash pruritic, rash pustular, rash vesicular, seborrheic dermatitis, skin exfoliation, palmar-plantar erythrodysesthesia syndrome, recall phenomenon	Actinic keratosis, arthropod bite/sting, dry skin, All PTs containing "Eczema", folliculitis, urticaria, skin abrasion; skin lesion, skin striae, skin toxicity, incision site rash, injection site rash, injection site erythema, catheter site erythema, puncture site erythema; dry skin; skin induration, skin toxicity, miliaria, psoriasis, acne, anal blister, blister, blister rupture
Renal insufficiency	Acute kidney injury, blood creatinine increased, chronic kidney disease, renal disorder, renal failure, renal impairment	
Respiratory tract infection[a]	Influenza like illness, Respiratory Syncytial Virus infection, respiratory tract infection	Upper respiratory tract infection, Lower

FDA Grouped PT	Included	Not Included
		respiratory tract infection
Second primary malignancy	Angioimmunoblastic T-cell Lymphoma, Chronic Myelomonocytic Leukemia, Gastric cancer, Myelodysplastic Syndrome, Pancreatic carcinoma, Squamous cell carcinoma of lung, intraductal papillary mucinous neoplasm, lung neoplasm, neoplasm skin	Lymphoma transformation, benign neoplasm, large intestine benign neoplasm
Sepsis	Bacteremia, Klebsiella bacteremia, sepsis, septic shock, Staphylococcal bacteremia, urosepsis	
Thrombocytopenia	Thrombocytopenia, Platelet count decreased	
Thrombosis or thromboembolism	Deep vein thrombosis, embolism, jugular vein thrombosis, pulmonary embolism, thrombosis, venous thrombosis	Superficial thrombosis
Transaminase elevation	Alanine aminotransferase increased, Aspartate aminotransferase increased, Transaminase increased, liver function test increased	PTs under FDA's "Hepatitis"
Upper respiratory tract infection	Acute sinusitis, laryngitis, nasopharyngitis, pharyngitis, rhinitis, rhinovirus infection, sinusitis, upper respiratory tract infection, upper respiratory tract infection bacterial, viral upper respiratory tract infection	Rhinitis allergic, rhinorrhea, upper-airway cough syndrome, PTs under FDA's "Respiratory Tract Infection" , nasal congestion, sinus congestion
Urinary tract infection	bacterial pyelonephritis, pyelonephritis, Escherichia urinary tract infection, Urinary tract infection, urinary tract infection enterococcal, urinary tract infection fungal, urinary tract infection pseudomonal, cystitis	Urosepsis, bacteriuria
Vision Changes	Blindness, diplopia, Vision blurred, visual impairment,	Glaucoma, intraocular pressure increased, dry eye, cataract, vitreous detachment, xerophthalmia, vitreous floaters

FDA Grouped PT	Included	Not Included
Vomiting	Vomiting	

Source: FDA analysis

[a] This grouping defines respiratory tract infection (RTI) of unspecified localization. Where designated, FDA also evaluated all "RTI" including the "Upper RTI" and "Lower RTI" grouping.

BLA 761324				

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Nonclinical Reviewer	Michael Manning, PhD	DHOT	Sections: 5	Select one: ☑ Authored ☐ Approved
	Signature: Michael L. Manning -S			Digitally signed by Michael L. Manning -S Date: 2023.04.20 16:40:39 -04'00'
Nonclinical Team Leader	Brenda Gehrke, PhD	DHOT	Sections: 5	Select one: ☑ Authored ☑ Approved
	Signature: Brenda Gehrke -S			Digitally signed by Brenda Gehrke -S Date: 2023.04.20 16:55:09 -04'00'
Nonclinical Team Deputy Division Director	Haleh Saber, PhD, MS	DHOT	Sections: 5, 14	Select one: ☐ Authored ☑ Approved
	Signature: Haleh Saber -S			Digitally signed by Haleh Saber -S Date: 2023.04.20 17:13:56 -04'00'
Clinical Pharmacology Reviewer	Sriram Subramaniam, PhD	OCP/DCPI	Sections: 6, 19.4	Select one: ☑ Authored ☐ Approved
	Signature: Sriram Subramaniam -S			Digitally signed by Sriram Subramaniam -S Date: 2023.04.21 10:06:12 -04'00'
Clinical Pharmacology Team Leader (Acting)	Xiling Jiang, PhD	OCP/DCPI	Sections: 6, 19.4	Select one: ☑ Authored ☑ Approved
	Signature: Xiling Jiang -S			Digitally signed by Xiling Jiang -S Date: 2023.04.21 10:11:12 -04'00'
Clinical Pharmacology Division Director	Brian Booth, PhD	OCP/DCPI	Sections: 6, 15, 19.4	Select one: ☐ Authored ☑ Approved
	Signature: Brian P. Booth -S			Digitally signed by Brian P. Booth -S Date: 2023.04.21 11:20:49 -04'00'
Pharmacometrics Reviewer	Robyn Konicki, PharmD	OCP/DPM	Sections: 6, 19.4	Select one: ☑ Authored ☐ Approved
	Signature: Robyn E. Konicki -S			Digitally signed by Robyn E. Konicki -S Date: 2023.04.21 10:15:20 -04'00'
Pharmacometrics Associate Director	Jiang Liu, PhD	OCP/DPM	Sections: 6, 19.4	Select one: ☑ Authored ☑ Approved
	Signature: Jiang Liu -S			Digitally signed by Jiang Liu -S Date: 2023.04.21 10:24:48 -04'00'

Associate Director for Labeling	Elizabeth Everhart, MSN, RN, ACNP	OOD	Sections: 11	**Select one:** ☑ Authored ☐ Approved
	Signature: Elizabeth E. Everhart -S		Digitally signed by Elizabeth E. Everhart -S Date: 2023.04.20 15:45:31 -04'00'	
Clinical Reviewer	Nicole Sunseri, MD, PhD	OOD/DHM II	Sections: All	**Select one:** ☑ Authored ☐ Approved
	Signature: Nicole R. Sunseri -S		Digitally signed by Nicole R. Sunseri -S Date: 2023.04.24 09:28:11 -04'00'	
Clinical Team Leader	Nicholas Richardson, DO, MPH	OOD/DHM II	Sections: All	**Select one:** ☐ Authored ☑ Approved
	Signature: Nicholas C. Richardson -S		Digitally signed by Nicholas C. Richardson -S Date: 2023.05.15 10:31:33 -04'00'	
Statistical Reviewer	Mingyu Xi, PhD	OB/DBIX	Sections: 7, 8	**Select one:** ☑ Authored ☐ Approved
	Signature: Mingyu Xi -S		Digitally signed by Mingyu Xi -S Date: 2023.04.21 11:33:07 -04'00'	
Statistical Team Leader	Zhiheng Xu, PhD	OB/DBIX	Sections: 7, 8	**Select one:** ☑ Authored ☑ Approved
	Signature: Zhiheng Xu -S		Digitally signed by Zhiheng Xu -S Date: 2023.04.23 08:36:10 -04'00'	
Cross-Disciplinary Team Leader (CDTL)	Nicholas Richardson, DO, MPH	OOD/DHM II	Sections: All	**Select one:** ☑ Authored ☑ Approved
	Signature: Nicholas C. Richardson -S		Digitally signed by Nicholas C. Richardson -S Date: 2023.05.15 10:32:15 -04'00'	
Division Director (Clinical)	Nicole Gormley, MD	OOD/DHM II	Sections: All	**Select one:** ☐ Authored ☑ Approved
	Signature: Nicole J. Gormley -S		Digitally signed by Nicole J. Gormley -S Date: 2023.05.15 11:21:41 -04'00'	
Supervisory Mathematical Statistician	Jonathon Vallejo, PhD	OB/DBIX	Sections: All	**Select one:** ☐ Authored ☑ Approved
	Signature: Jonathon J. Vallejo -S		Digitally signed by Jonathon J. Vallejo -S Date: 2023.04.24 09:00:23 -04'00'	
Office Director or signatory (NME only)	Marc R. Theoret, MD		Sections: All	**Select one:** ☐ Authored ☑ Approved
	Signature:			

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

NICHOLAS C RICHARDSON
05/19/2023 09:10:11 AM

MARC R THEORET
05/19/2023 10:46:12 AM
My signature indicates that I have considered the FDA assessments and recommendations included in this Review in determining the regulatory action.